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WHY DO CLASSIFICATIONS CHANGE? LESSONS LEARNED FROM LIPOSARCOMA

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The classification of soft tissue tumors has undergone massive transformation over the past several decades, for a variety of reasons. One of the most important factors driving these changes has been advances in our understanding of the molecular genetics of soft tissue neoplasms, which has resulted in the identification of new tumor types, abandonment of previously widespread terminology, and recognition of new connections between established entities. Few tumor types illustrate the impact of advances in molecular genetics better than liposarcoma, whose classification has changed significantly since the publication of the 2002 WHO classification. This lecture will review established, newly described and abandoned subtypes of liposarcoma, and discuss the ways in which advances in our understanding of the clinical, morphological and molecular genetic features of these tumors has led to improved understanding, and more rational classification. In the second part of the lecture, the differential diagnosis of the most common liposarcoma subtype, well-differentiated liposarcoma, will be discussed in detail.

Keywords: liposarcoma, molecular genetics, immunohistochemistry.

A MORPHOLOGY-BASED APPROACH TO THE IDENTIFICATION OF SELECTED SOFT TISSUE TUMORS WITH CHARACTERISTIC MOLECULAR GENETICS

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Although morphological evaluation remains the cornerstone for the diagnosis of soft tissue tumors, identification of underlying molecular genetic events plays an increasingly important role in this process. This is problematic for many pathologists, as access to molecular genetic techniques is not universal (in any country). Thankfully, our improved understanding of the molecular pathogenesis of soft tissue tumor has simultaneously allowed us to refine and improve our understanding of the morphological and immunophenotypically features of many soft tissue entities, and in some instances to create immunohistochemical "surrogates" for molecular genetic tests. During this slide seminar we will discuss 10 unusual soft tissue tumors of various lineages, all of which harbor specific molecular genetic events, and all of which can be correctly diagnosed in almost all instances *without* molecular genetic testing, if one is aware of their characteristic morphological and immunohistochemical features.

Keywords: liposarcoma, molecular genetics, immunohistochemistry.

IMAGING OF SOFT TISSUE TUMORS: KEY INSIGHTS FOR PATHOLOGISTS

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Imaging plays a pivotal role in the detection, characterization, and management of soft tissue tumors and has a direct impact on pathological interpretation and multidisciplinary decision-making. It is often the first step in tumor evaluation, providing essential contextual information before biopsy or histological assessment. Awareness of imaging features enables pathologists to anticipate tumor type, select appropriate tissue sampling sites, and interpret unusual or heterogeneous histologic findings within the correct clinical and radiologic context.

Imaging significantly narrows the differential diagnosis, guides biopsy planning and sample selection, and helps explain histologic variability. Plain radiography, although often overlooked, remains a valuable first-line modality, providing important information on calcifications, ossification, chondroid or osteoid matrix, subtle bone changes, and periosteal reaction.

Ultrasound is a rapid, non-invasive tool for the evaluation of superficial soft tissue tumors, though it is less effective for deep-seated lesions. It is particularly useful for distinguishing cystic from solid masses, assessing vascularity, and planning and guiding core needle biopsy.

Computed tomography (CT) allows precise assessment of calcifications and mineralization, evaluation of bone involvement, and accurate staging. It is especially valuable in retroperitoneal sarcomas and in cases where osseous involvement is suspected.

Magnetic resonance imaging (MRI) is the cornerstone of soft tissue tumor assessment. Owing to its superior soft tissue contrast, MRI provides detailed information on lesion extent, fascial involvement, relationships to adjacent structures, and tissue composition, including fat, myxoid components, and necrosis—features that are critical for pathological correlation.

This presentation will highlight key imaging features on different imaging modalities and their pathological implications in the differentiation of benign lipoma from sarcoma, atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL), myxoid versus fibroblastic tumors, synovial sarcoma in comparison with peripheral nerve sheath tumors and vascular tumors, tumor-like lesions etc.

In conclusion, imaging provides indispensable context for pathological interpretation. Radiologic features often predict tumor type and grade, refine the differential diagnosis prior to biopsy, and support accurate staging and management. Close collaboration between radiologists and pathologists is essential to optimize diagnostic accuracy and improve patient outcomes

Keywords: Imaging, ultrasound, MRI, CT

CELL BLOCKS AND IMMUNOCYTOCHEMISTRY IN ROUTINE FINE NEEDLE ASPIRATION OF NECK LYMPH NODES AND SOFT TISSUES

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Background:
Fine-needle aspiration cytology (FNAC) is a minimally invasive, cost-effective, and rapid diagnostic tool widely applied for the evaluation of cervical lymph nodes and soft tissue masses. FNAC allows for differentiation between inflammatory, benign, and malignant lesions, guiding treatment planning. However, conventional smears may provide limited material for ancillary studies, especially in lymphoproliferative disorders, metastatic carcinoma of unknown origin, and diagnostically challenging soft tissue tumors.
Methods:
Cell block (CB) technique was used to process residual FNAC material into paraffin blocks, enabling preparation of multiple sections for immunocytochemistry (ICH) and molecular testing. The method was applied to more than 3,000 cases over the last 10 years, including lymphadenopathy and soft tissue tumors.
Results:
The use of CB and ICH significantly increased diagnostic yield. In lymphoproliferative disorders, accurate diagnosis and subclassification were achieved in most cases by combining cytomorphology with ICH. For metastatic carcinomas of unknown origin, the primary tumor site was identified in the majority of patients. In soft tissue pathology, CB allowed the use of lineage-specific immunomarkers, leading to more accurate classification, grading, and prognostic assessment. Furthermore, biomarker analysis for targeted therapy (ER, PR, HER2, CD20, EGFR, CD117) was successfully performed, facilitating personalized treatment strategies.
Conclusion:
The integration of FNAC, CB, and ICH provides a highly effective diagnostic approach for cervical lymphadenopathy and soft tissue tumors. This combined methodology improves diagnostic accuracy, supports prognostic evaluation, and guides therapy selection, including targeted treatments. It should be considered a standard component of the diagnostic work-up in such patients.

Keywords: cell block, FNA smears, immunocytochemistry.

WHOOPS PROCEDURES IN SOFT TISSUE SARCOMA MANAGEMENT: WHY MARGINS MATTER

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Unplanned excisions of soft tissue sarcomas, commonly referred to as "whoops procedures," remain a significant challenge in the management of these rare tumors. They usually occur when a soft tissue mass is presumed to be benign and removed without appropriate preoperative diagnostic work-up, staging, or multidisciplinary planning. As a result, these procedures often leave behind microscopic or even macroscopic residual disease, substantially increasing the risk of local recurrence and compromising patient outcomes.

The incidence of whoops procedures is reported to range between 20–50% of all soft tissue sarcoma cases in certain series, underlining the need for better awareness among general surgeons and orthopedic surgeons. Once a whoops procedure has been performed, the standard of care involves referral to a specialized sarcoma center and consideration of a wide re-excision of the surgical bed. Such re-excisions have been shown to reveal residual tumor in up to 60–80% of cases, highlighting the inadequacy of the initial margins.

Surgical margins are a critical determinant of local control and long-term survival in soft tissue sarcomas. Wide, negative margins (R0) are associated with significantly lower recurrence rates compared to marginal (R1) or intralesional (R2) resections. Following a whoops procedure, achieving appropriate margins can be technically challenging due to distortion of normal anatomy, contamination of multiple tissue planes, and previous wound complications. In such scenarios, a balance must be struck between radical surgery and preservation of function, with multimodal strategies including radiotherapy or chemotherapy often required to optimize outcomes.

Ultimately, prevention of whoops procedures lies in early recognition of suspicious soft tissue masses and prompt referral to sarcoma centers before any surgical intervention. Multidisciplinary evaluation, preoperative imaging, biopsy, and careful surgical planning are essential steps to ensure oncologically adequate resections. Raising awareness of this issue is crucial in improving the prognosis and quality of life of patients with soft tissue sarcomas.

Keywords: whoops procedure, soft tissue sarcoma, residual disease, surgical margins.

EMERGING THERAPEUTIC STRATEGIES FOR SOFT TISSUE SARCOMA: INTEGRATING TARGETED THERAPY, IMMUNOTHERAPY AND ADVANCED RADIOTHERAPY

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Soft tissue sarcomas (STS) represent a heterogeneous group of malignancies with limited treatment options and suboptimal outcomes in advanced stages. Recent therapeutic innovations are reshaping the management landscape, offering new hope for improved survival and quality of life. Targeted therapies such as antibody–drug conjugates (ADCs) deliver cytotoxic payloads directly to tumor cells, minimizing systemic toxicity. Immunotherapeutic approaches, including immune checkpoint inhibitors (ICIs) and adoptive cell therapies, are harnessing and reprogramming the patient's immune system to recognize and eradicate malignant cells. In parallel, radiotherapy techniques are evolving beyond conventional fractionation. Spatially fractionated grid radiation therapy (SFGRT) offers the potential for selective tumoricidal effects while sparing surrounding normal tissues. Additionally, prophylactic lung irradiation is under preliminary investigation as a strategy to eradicate occult micrometastatic disease and delay pulmonary relapse, a common site of STS progression. These modalities, alone or in combination, promise a shift toward more personalized, biology-driven treatment algorithms. This abstract reviews the current evidence supporting these novel approaches, highlights early clinical trial results, and discusses challenges related to patient selection, toxicity management, and integration into multimodal care. The future of STS therapy lies in leveraging synergistic strategies to optimize local control and systemic disease management.

Keywords: sarcoma, soft tissue, treatment strategies, immune checkpoint inhibitors.

CANCER DRUG DISCOVERY AND DEVELOPMENT IN THE ERA OF PERSONALIZED MOLECULAR MEDICINE

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Personalized molecular medicine is revolutionizing cancer drug discovery by enabling the development of targeted therapies tailored to the unique molecular alterations in individual tumors. This approach is significantly improving treatment outcomes and disease prognosis. Advances in sequencing technologies have greatly enhanced our understanding of the mutational landscape of human cancers and revealed the genetic drivers in specific tumors.
In this talk, I will outline our efforts to develop potential therapeutics by focusing on druggable mutations and targeted modalities, including small-molecule inhibitors and targeted protein degraders. I will also discuss the integration of functional assays with genomics to further enhance the effectiveness of personalized cancer medicine.
Cancer cells exhibit distinct characteristics, known as hallmarks, including the ability to evade apoptosis, or programmed cell death, through overexpression of anti-apoptotic proteins from the Bcl-2 family. These proteins have become promising therapeutic targets across multiple cancer types, with Venetoclax, a selective Bcl-2 inhibitor, being the first approved drug in this category.
This presentation will share findings from our investigation of Bcl-2 survival dependence across a range of cancers, including both hematologic and solid tumors. Using functional diagnostic BH3 profiling assays, we tested both established cell lines and primary patient samples. Our results show that hematologic cancers rely on Bcl-2 and/or Mcl-1 proteins, while most solid tumors co-depend on Bcl-xL and Mcl-1 anti-apoptotic proteins. By combining functional assays with genomic data, we can develop more precisely tailored molecularly targeted treatments, improving the effectiveness of personalized medicine and the prediction of patient responses to therapy.

Keywords: personalized medicine, cancer drug discovery.

MOLECULAR LANDSCAPE OF PEDIATRIC NEOPLASMS IN MACEDONIA

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Introduction

Pediatric neoplasms represent a diverse group of malignancies with varying incidence and molecular profiles. Leukemias, particularly acute lymphoblastic leukemia (ALL), account for approximately 26% of pediatric cancers, making them the most common, followed by central nervous system (CNS) tumors (e.g., medulloblastomas and gliomas) at about 16%, and other solid tumors such as neuroblastomas, Wilms tumors, and rhabdomyosarcomas, each contributing 5-10% to the overall incidence. These tumors exhibit unique molecular characteristics distinct from adult malignancies, driven by specific genetic alterations, epigenetic modifications, and dysregulated signaling pathways. This study explored the molecular landscape of pediatric neoplasms in Macedonia, integrating advanced genomic profiling to uncover key mutations, epigenetic changes, and potential therapeutic targets, aiming to enhance precision diagnostics and personalized treatment strategies for pediatric patients in Macedonia.

Materials and methods

The study includes results from 65 patients with ALL (55 B-ALL, 10 T-ALL) diagnosed in a period of 6 years, and 20 patients with solid neoplasms (6 patients with CNS tumors, 5 patients with neuroblastoma, 3 patients with lymphoma, 2 patients with Wilms tumor and 1 patient with rhabdomyosarcoma, Ewing's sarcoma, chondrosarcoma and Langerhans cell histiocytosis, each) diagnosed in a period of 2 years. Conventional and advanced molecular techniques were used to characterize the genetic landscape and monitor treatment response in these patients. The diagnosis of the patients with ALL was determined by initial screening for clonal immunoglobulin (Ig) and T-cell receptor (TCR) gene rearrangements according to the BIOMED-2 protocol, using multiplex PCR followed by fragment analysis with capillary electrophoresis (CE). The clonal rearrangements were confirmed by Next-Generation Sequencing (NGS), which was also used to detect minimal residual disease (MRD) with a sensitivity of 0.01% at crucial time-points. Detection of disease-related abnormalities such as chromosomal translocations (e.g., ETV6::RUNX1, BCR::ABL1), aneuploidies and copy number variations (CNVs) in specific disease-related genes (e.g., IKZF1, CDKN2A/B, PAX5) was performed using quantitative reverse transcription PCR (qRT-PCR) and multiplex ligation-dependent probe amplification (MLPA). Whole-exome sequencing (WES) was performed on paired diagnosis and relapse samples from patients with relapse to identify genetic alterations associated with disease progression. The molecular characterization of the other pediatric neoplasms was conducted using the TruSight Oncology 500 (TSO 500) assay from Illumina which detects genetic changes in 523 genes with a sensitivity 1-5%, including RNA variants in 55 genes and low-density genome-wide CNVs covering crucial cancer-related regions. Variant calling was performed using DRAGEN TruSight Oncology 500 Analysis Software, with variants annotated using Illumina Connected Annotations and sources including JAX-CKB, OncoKB, COSMIC, ClinVar, CancerHotspots, and gnomAD.

Results
The genetic characterization of the patients with ALL identified a diverse landscape of chromosomal and molecular abnormalities, particularly in B-ALL, where hyperdiploidy (>50 chromosomes) was prevalent (33%, n=18/55). Common fusion transcripts in B-ALL included ETV6::RUNX1 (15%, n=8/55), and TCF3::PBX1 (7%, n=4/55). These abnormalities correlated with standard risk stratification per protocol guidelines, though only 3/7 relapse cases were initially high-risk based on such features. Further analysis highlighted recurrent deletions and amplifications in key lymphoid development and tumor suppressor genes, predominantly in B-ALL, where 88% of the patients harbored at least one CNV. The most common variation was PAR1 (CRLF2, CSF2RA, IL3RA) duplication observed in 38% of patients, followed by CDKN2A/2B deletions in 28% and PAX5 deletions in 22%. IKZF1 gene deletions occurred in 10% of cases, none of which exhibited the IKZF1plus profile. Other variations included deletions of ETV6 (12%), BTG1 (6%), RB1 (6%), and EBF1 (2%), as well as TP53 (4%) and ATM1 (6%) deletions. In T-ALL, CDKN2A/B deletions were detected in 50% and IKZF1 deletions in 20% of cases, one of which with IKZF1plus profile. The analysis of 6 paired diagnosis-relapse samples revealed mutations in the CREBBP gene in 4 of the patients with relapse, either present from the disease onset or acquired at relapse, while none of the examined patients in remission presented alterations in this gene. Deletions in TP53 and EBF1 (present in 2/6 and 1/6 of the patients with relapse, respectively) were also infrequent or absent in the patients in remission. The comprehensive genetic characterization of the patients with solid tumors identified diverse changes in these patients relevant for their diagnosis, prognosis and therapy response. Among the diagnostic variants, amplification of MYCN was most common (3/5 patients with neuroblastoma), followed by variants in several genes widely known for a specific diagnosis (EWSR1::FLI1 in Ewing sarcoma, BRAF in Langerhans cell histiocytosis, and EGFR vIII transcript, PTEN, ATRX, NF1 and H3-3A in glioblastomas). The patients with neuroblastoma were characterized by multiple CNVs, some of them associated with more aggressive form of the disease (17q+, 1p-, 2p+, 11q-). Overall, diagnosis-related markers were identified in 8 out of 20 patients, prognostic markers in 11 out of 20 patients and markers predictive for a specific therapy in 7 out of 20 patients, only one of them presenting strong clinical evidence (Tier1A). Potentially germline variants were identified in 7 patients, and two of them were characterized as incidental findings (PRKN variant associated with Parkinson’s disease and MPL variant associated with myeloproliferative neoplasms).
Conclusion
These findings underscore the prognostic heterogeneity of genetic lesions in Macedonian pediatric neoplasms, advocating integration of CNV and mutation profiling beyond standard genetic alterations to broaden the prognostic marker portfolio, refine the stratification in these patients and identify known and potential therapeutic targets leading to a more personalized treatment.

Keywords: pediatric neoplasms, prognostic markers, molecular analysis.

NOVEL MOLECULAR DIAGNOSTIC APPROACHES FOR TARGETABLE MUTATIONS IN COLORECTAL CANCER: A FIVE-YEAR RETROSPECTIVE STUDY

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Introduction:
Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide. Over the past two decades, significant improvements in response rates (RR), progression-free survival (PFS), and overall survival (OS) have been achieved as a result of the development of novel therapeutic agents targeting genetic events involved in colorectal carcinogenesis.
Objectives:
The aim of this study was to perform genetic profiling of patients with CRC in North Macedonia who were treated between March 2021 and February 2025 at the University Clinic for Oncology and Radiotherapy, University Clinical Center Skopje. Genetic alterations in two or more of the most frequently mutated CRC-associated genes—KRAS, BRAF, PIK3CA, NRAS, EGFR, and DPYD—were analyzed, along with microsatellite instability (MSI) status.
Materials and methods:
Real-time polymerase chain reaction (RT-PCR) was used to detect alterations in KRAS, EGFR, NRAS, BRAF, PIK3CA, and DPYD, while fragment analysis was applied for MSI testing. Statistical analyses were performed to further investigate the presence and significance of potential associations between genetic alterations and clinical parameters.
Results and discussion:
Out of 717 patients with CRC, 225 patients (31.38%) harbored at least one somatic variant, of whom 36 patients (5.02%) presented with two concurrent mutations. KRAS mutations were the most frequent, with 14 distinct variants identified in 46.60% of patients, followed by PIK3CA (8.99%), BRAF (6.72%), and NRAS (5.30%).
Among patients with PIK3CA alterations, 69.44% also carried concurrent KRAS mutations. Additionally, 11.11% exhibited co-occurring KRAS/BRAF, two KRAS/NRAS, and two BRAF/PIK3CA mutations. Finally, statistical analysis revealed a significant association between PIK3CA alterations and patient sex.
Conclusion:
The findings of this study contribute to a deeper understanding of CRC molecular characteristics and the identification of key oncogenic drivers. These results may facilitate the development of improved diagnostic approaches and support the implementation of novel personalized therapeutic strategies for CRC patients in North Macedonia.

Keywords: colorectal cancer, molecular characteristics.

FIVE YEARS OF LUNG CANCER PATHOLOGY AND MOLECULAR DATA - SINGLE CENTRE EXPERIENCE

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Background:
Lung cancer remains the leading cause of cancer-related mortality worldwide. Understanding histological distribution and molecular alterations is essential for optimizing diagnosis and treatment strategies.
Methods:
We retrospectively analysed 1,179 patients diagnosed with lung cancer over five years at Institute of Pathology, Faculty of Medicine - Skopje. Clinicopathological and molecular data were collected and evaluated.
Results:
Most of the patients in our study were males, 780 (66.2%), with male-to-female ratio of nearly 2:1. Most patients were diagnosed in their sixth and seventh decades; only 2.1% were younger than 40 years. Squamous cell carcinoma (SQCC) was the most frequent subtype (42.4%), followed by adenocarcinoma (38.5%) and small cell carcinoma (12.6%). Adenocarcinoma was more common in women and presented at earlier stages, whereas squamous and small cell carcinomas predominated in men and were diagnosed at more advanced stages.
KRAS mutations were the most frequent, identified in 27% of the patients, followed by MET (5,7%), EGFR (5,2%) and RET (4,3%). ALK and ROS rearrangements were found in 4,83% and < 1% of the cases, respectively. KRAS, RET and MET mutations as well as ALK and ROS1 rearrangements, were largely restricted to adenocarcinoma and enriched in female patients. PD-L1 was slightly more positive in SQCC vs adenocarcinoma with TPS ≥1%, and adenocarcinoma was slightly more positive with TPS ≥50%. Males had modestly higher PD-L1 positivity than females.
Conclusion:
Our results revealed histological and molecular heterogeneity in lung cancer patients, with actionable alterations concentrated in adenocarcinoma, underscoring the importance of integrated pathology and biomarker testing for personalized lung cancer management.

Keywords: lung cancer, molecular alterations, histologic types.

HISTOLOGICAL AND MOLECULAR CLASSIFICATION OF SCLC

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Small cell lung carcinoma (SCLC) is a high-grade neuroendocrine carcinoma defined by its aggressiveness, poor differentiation and very poor prognosis. Histological characteristics of SCLC are a dense cell arrangement, scant cytoplasm, dense core granules, and lack of significant nucleoli, high proliferation rate and very high Ki-67 proliferation and positive NE markers including synaptophysin, chromogranin A and insulinoma-associated protein 1 INSM1. However, a few SCLC specimens were negative for all standard NE markers and therefore could not be correctly classified. The current histological sub-classification recognizes two subtypes: pure SCLC and combined SCLC. New classification was proposed in 2019 to divide SCLC into four molecular subtypes (NEUROD1, ASCL1, POU2F3, and YAP1 (NAPY). The roles of transcription factors in shaping tumor behavior and regulating the various different NE patterns of SCLCs have recently been elucidated. ASCL1 and NEUROD1 are two master transcription factors that govern neuroendocrine (NE) differentiation. Recently, two additional master transcription factors, POU2F3 and YAP1, were identified, and the SCLC lines expressing one of these two genes lack the NE features. The molecular subclassification of SCLC is not practically useful for treatment selection. In the near future, with the development of molecular target therapies, the immunohistochemical application of crucial molecules in tissue samples will provide valuable information for the assessment of cell biological and therapeutic issues in the diagnosis of SCLC.

Keywords: small cell carcinoma, molecular classification, immunohistochemistry.

COLORECTAL CANCER: BIOMARKERS THAT GUIDE THERAPY

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The goal of modern oncology is personalized therapy, which depends on a thorough understanding of tumor biology. Colorectal carcinoma (CRC) is a heterogeneous disease with molecular subtypes that influence prognosis and treatment response.
In clinical practice, the most commonly assessed biomarkers include KRAS, NRAS, and BRAF mutations, microsatellite instability (MSI), and the expression of PD-L1 and HER2 proteins. These markers are especially relevant in advanced CRC, but are increasingly applied in earlier stages.
KRAS mutations, found in 35–45% of CRC, drive constitutive MAPK pathway activation and resistance to anti-EGFR therapy. BRAF mutations, most often V600E (8–12%), are linked to poor prognosis and limited response to standard therapies. They occur more frequently in MSI-high tumors and in the serrated pathway of carcinogenesis. KRAS and BRAF mutations are mutually exclusive.
Microsatellites are repetitive DNA sequences prone to replication errors, corrected by the mismatch repair (MMR) system involving MLH1, PMS2, MSH2, and MSH6. Loss of one or more proteins, detected by immunohistochemistry, indicates MMR deficiency (dMMR) and strongly correlates with MSI. In unclear cases, RT-PCR directly confirms MSI. Patients with stage II CRC who are MSI-H/dMMR derive no benefit from adjuvant 5-fluorouracil. MSI/MMR testing also predicts response to immunotherapy and serves as a screening tool for Lynch syndrome in younger patients or those with family history of CRC.
In contemporary oncology, additional predictive biomarkers such as PD-L1 and HER2 are increasingly applied to guide targeted therapies, underscoring their essential role in personalized CRC management.

Keywords: colon cancer, microsatellite instability, biomarkers.

CHALLENGE OF MACROBIOPSY IN MOLECULAR DIAGNOSTICS

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Molecular diagnostics have become an integral part of modern pathology, providing the foundation for evidence-based and personalized medicine. Accurate molecular testing requires sufficient and high-quality tissue samples, which often poses a challenge when conventional biopsy techniques are employed. In this context, macrobiopsy - particularly with the use of spirotome devices - emerges as a valuable approach to obtaining larger, more representative specimens.

From the interventional radiology standpoint, the balance between diagnostic yield, patient safety, and procedural efficiency is crucial. While standard core needle biopsies can provide adequate histological material, their limitations in molecular analysis are increasingly evident, especially in complex oncologic cases where detailed genomic profiling is essential for therapeutic decision-making. Macrobiopsy allows pathologists to perform comprehensive analyses, including immunohistochemistry, next-generation sequencing, and other advanced molecular techniques, thereby reducing the risk of inconclusive results or the need for repeat procedures.

However, the use of macrobiopsy is not without challenges. Larger tissue acquisition carries potential risks such as bleeding, pain, or procedural complications, requiring meticulous planning and imaging guidance. Furthermore, not all anatomical sites are equally accessible, and the choice of biopsy technique must be individualized. Collaboration between interventional radiologists and pathologists is therefore essential to optimize diagnostic pathways.

In conclusion, macrobiopsy with spirotome devices represents an evolving tool that bridges interventional radiology and pathology, enabling more accurate molecular diagnostics and advancing personalized patient care. Integrating this approach into routine practice will be key to addressing the growing demands of precision oncology.

Keywords: macrobiopsy, spirotome biopsy, molecular diagnostics, evidence-based medicine, personalized medicine, interventional radiology

AI IN MOLECULAR PATHOLOGY - ALGORITHMS FOR VUS RECLASSIFICATION

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Artificial Intelligence (AI) is rapidly transforming molecular pathology, particularly in the classification of genetic variants identified through next-generation sequencing (NGS). A major challenge in clinical genomics is the interpretation of Variants of Uncertain Significance (VUS), which often lack sufficient evidence for definitive classification. The 2015 ACMG/AMP guidelines provide a structured framework for variant interpretation using 28 criteria across five classification categories. However, manual application of these guidelines is time-consuming, subjective, and prone to inconsistencies across laboratories. AI offers scalable, reproducible solutions by integrating genomic, phenotypic, and population data to automate and enhance variant classification. Machine learning tools such as AlphaMissense and REVEL have demonstrated improved sensitivity and specificity in reclassifying VUS, supporting more accurate and timely diagnostics. These tools contribute computational evidence within the ACMG framework, accelerating the reclassification process and reducing diagnostic uncertainty. Real-world applications, including disease-specific models and oncology studies, illustrate AI's potential to increase diagnostic yield and support personalized medicine. Furthermore, Bayesian modeling and gene-specific ACMG adaptations by expert panels (e.g., ClinGen) enhance the precision of AI-driven interpretations. The integration of AI into clinical workflows not only improves efficiency but also empowers clinicians with actionable insights, ultimately enhancing patient outcomes. As AI systems continue to evolve, their role in molecular pathology will become increasingly central to the future of precision medicine.

Keywords: Artificial Intelligence, Molecular Pathology, Variant Classification, ACMG/AMP Guidelines, Variants of Uncertain Significance (VUS), AlphaMissense, REVEL, Machine Learning, Clinical Genomics, Personalized Medicine.

MOLECULAR MECHANISMS OF GLYMPHATIC AND MENINGEAL LYMPHATIC DYSFUNCTION IN NEURODEGENERATIVE DISEASES: FROM IMPAIRED PROTEIN CLEARANCE TO THE FEASIBILITY OF MICROSURGICAL LYMPHATIC RECONSTRUCTION

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Neurodegenerative diseases (NDs), comprising frontotemporal dementia (FTD) and Alzheimer's disease (AD), are progressive disorders which are represented as pathological deposits of protein, loss of neurons, and cognitive decline. These disorders involve distinct, but also share overlapping molecular features and are currently grouped according to biomarker profiles.
AD is typically characterized by the existence of amyloid-beta (Aβ) plaques, tau neurofibrillary tangles, and neurodegeneration, while FTD includes a diversified range of disorders like tauopathies, TDP-43 proteinopathies, and in some cases, amyloid deposition. AD and FTD have common pathological mechanisms such as protein misfolding, synaptic dysfunction, neuroinflammation, oxidative stress, and impaired clearance of toxic aggregates. The accumulation of misfolded proteins is generally believed to arise from either their overproduction or their inadequate clearance.
In addition, the latest findings emphasize the failure of the brain's waste clearance systems, including the glymphatic and meningeal lymphatic pathways, as being the main contributor to the pathogenesis and progression of these diseases.
Glymphatic system disfunction may be the primary element of the pathophysiology of neurodegenerative diseases, as a result of impaired clearance mechanisms, which in turn results in the formation of toxic protein clusters in neurons leading to their degeneration. Though the main mechanisms are quite different depending on the disease, the common factors implicated in the glymphatic dysfunction that leads to aging and neurodegeneration are: AQP4 channels mislocalization, atherosclerosis and decreased arterial pulsatility, sleep disturbances and impaired glymphatic clearance.
Meningeal lymphatic vessels (MLVs) and deep cervical lymph nodes (dcLNs) maintain the process of interstitial fluid (ISF) dynamics. This lymphatic drainage network or the lymphatic system is crucial for the homeostasis of the CNS.
Recent research strongly supports lymphovenous anastomoses (LVAs) as a promising microsurgical intervention for improving central nervous system (CNS) waste clearance.
This innovative strategy is an alternative or an additional treatment to the conventional pharmacological methods for managing neurodegenerative diseases which are related to impaired glymphatic and gliolymphatic functions that lead to amyloid protein deposition, neuroinflammation, and fluid imbalance.

Keywords: glymphatic system, microsurgery, neurodegenerative diseases.

CONTEMPORARY CLASSIFICATION OF RENAL TUMORS - MORPHOLOGIC, MOLECULAR OR A COMBINATION OF BOTH?

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Recent advances have improved our understanding of the morphologic, immunohistochemical, molecular, epidemiologic and clinical characteristics of the renal tumors, which led to modifications in the new 2022 World Health Organization (WHO) classification of renal cell tumors (5th edition), based on the Genitourinary Pathology Society (GUPS) consensus work on existing entities and novel and emerging renal entities. Practicing pathologists and clinicians, such as urologists and uro-oncologists, should be knowledgeable and aware of these new developments on existing renal entities, and those pertaining to the novel renal tumors. The navigation through this complex and evolving field is challenging, but it crucially impacts patient care, particularly in environments with larger kidney tumor volumes, such as major academic centers, as well as in settings with more limited resources. An accurate diagnosis of renal tumors will further reduce the category of "unclassifiable renal carcinomas/tumors" and will lead to better clinical management and improved patient prognostication.
In this lecture, we aim to provide an overview and outline the changes in the WHO classification 2022 (5th edition) of renal tumors. We will highlight the features and the clinical relevance of several novel and more recently described renal entities and we will emphasize and illustrate the congruence of the contemporary morphologic and molecular classification of renal tumors. We will also provide an understanding for the rationale for terminological changes (i.e. introduction of novel nomenclature) for some existing entities and we will describe the evolving molecular aspects and concepts in classifying renal tumors. Finally, we will highlight the key role that morphology and immunohistochemistry have as primary tools for the diagnosis of renal tumors.

Keywords: kidney tumors, rare entities, classification.

PROSTATE CANCER - DIAGNOSIS, GRADING AND REPORTING - WHAT'S IMPORTANT AND WHY

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Prostate cancer is one of the commonest cancers in men worldwide. Almost 60 years ago, the pathologist Donald Gleason developed a grading system for prostatic adenocarcinoma, which was embraced almost universally as an essential component of prostate adenocarcinoma grading and reporting. Over time, the system has been modified and despite the modifications in the past, this grading system has been validated as a fundamental prognostic factor for prostate cancer, both on biopsy and on radical prostatectomy for patient outcomes, including biochemical failure, local recurrence and lymph node or distant metastasis. Gleason score has also been incorporated into clinical tools, such as clinical nomograms, which are used to predict pathologic stage and outcome following surgery or radiotherapy. In this lecture we will provide a brief overview of the general epidemiological features of prostate cancer. We will highlight the technical issues important to facilitate the diagnostic assessment of prostate biopsies. We will review the diagnostic work-up of prostate needle biopsy specimens and the diagnostic criteria for prostate cancer, as well as the principles and the evolution of the grading system, particularly the more recent ones, including a better definition of the grading patterns and the modifications introduced by the new grading system, as well as other important issues, such as cribriform/intraductal carcinoma, and the impact and reporting of MRI-targeted needle biopsy. We will highlight some of the recent recommendations for prostate cancer reporting introduced by the international organizations, such as the Genitourinary Pathology Society (GUPS) and International Society of Urologic Pathology (ISUP). We will briefly cover the common benign conditions that can mimic prostate cancer (false positive), as well as the unusual deceptive patters of prostate cancer (false negatives). Lastly, we will review the important parameters of systematic prostate cancer reporting on needle core biopsy and radical prostatectomy.

Keywords: prostate cancer, diagnostic pitfalls, grading system.

PRACTICAL ISSUES IN DIAGNOSING AND REPORTING UROTHELIAL URINARY BLADDER CARCINOMA

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In this lecture, we will cover the practical diagnostic and reporting issues of urothelial carcinoma that pathologists face in their daily practice. We will provide an introduction of the normal anatomy and histology of the urinary bladder and we will address the technical issues of specimen handling and sampling. We will also address and explain the need for a systematic reporting with established diagnostic and prognostic elements and the rationale for it. We will also cover the recent updates from the WHO 2022 classification, regarding the changes and nomenclature alterations regarding urothelial carcinoma. We will describe the key elements and criteria for urothelial cancer grading, and we will describe the principles of the introduced molecular classification for muscle-invasive urothelial cancer. We will describe the different growth patterns of urothelial carcinoma (papillary, flat, inverted) with emphasis of the spectrum of flat lesions, including benign, preinvasive (in-situ) and invasive lesions. We will briefly review the common and relevant urothelial cancer subtypes and the necessity for their correct diagnosis. Lastly, we will review the criteria and the principles of urothelial carcinoma staging, including the need for a systematic approach to correct staging and prognostication. Throughout the lecture we will use practical examples to illustrate the discussion points, regarding grading, staging, and appropriate use of immunohistochemistry, particularly for the evaluation of flat lesions and urothelial carcinoma subtypes.

Keywords: bladder cancer, immunohistochemistry, grading.

PATHOLOGIC-RADIOLOGIC CORRELATION OF PROSTATE CARCINOMA IN EVERYDAY PRACTICE

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Introduction:
The challenges of prostate carcinoma diagnosis in everyday practice in some cases are great and the pathologists sometimes need to rely on additional information, particularly radiology reports.
Material and methods:
We present several cases where the pathologic radiologic correlation was vital or important in establishing the correct diagnosis.
All the cases were either core biopsy specimens or radical prostatectomy specimens. All specimens were formalin fixed, paraffin embedded and routinely stained with Hematoxylin-Eosin. In some cases, immunohistochemical analysis was performed to ensure the correct diagnosis using the antibodies AMACR, CK34betaE12, Androgen Receptor, Progesterone Receptor, Vimentin, CD34, bcl-2, Desmin, CD99, CKAE1/AE3, EMA and c-kit.
Results and discussion:
The pathologists' concern of radiology reports was multifold. The greatest need for information was the localization of the lesion. Then, other important parameters were the size of the lesion and the relationship of the lesion with the surrounding structures. In several cases we will show how the radiologic suspicion for the type of the lesion led to assurance for the correct pathohistological diagnosis. Rare cases demanded thorough radiological and pathological correlation. Also, various types of lesions in the same prostate were correlated with a different radiological interpretation of these lesions.
Conclusion:
The necessity for a close pathologic radiologic correlation arose when difficult or dubious cases were presented to the pathologists for final diagnosis. Also, dubious radiological interpretation led the radiologists to address these issues to the pathologists and that yielded an interesting debate. These challenging cases emphasized the close interdependence of these two fields of medicine that are closely related.

Keywords: pathologic-radiologic correlation, prostate carcinoma, immunohistochemistry.

GUIDELINES FOR THE PATHOLOGIC ASSESSMENT OF NEPHRECTOMY SPECIMENS IN RENAL CELL CARCINOMA

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Introduction:
Renal malignancies represent a significant proportion of visceral tumors and are major contributors to cancer-related mortality worldwide. Partial or radical nephrectomy remains the gold standard for renal tumors. Accurate specimen handling by urologists and pathologists is fundamental to optimal clinical management and prognostic evaluation.
Methods and Results:
Structured reporting templates developed by expert pathology panels provide standardized frameworks for consistent macroscopic dissection and pathological interpretation of renal tumors, offering improved readability and information accessibility for urologists compared to traditional narrative reports.
Conclusion:
This review summarizes the required and recommended components of standardized evaluation protocols for tumors of renal tubular origin in nephrectomy specimens, aiming to achieve uniform reporting, enhance diagnostic accuracy, improve clinical decision-making, and support international research collaboration.

Keywords: structured cancer protocol; nephrectomy; renal cell carcinoma; macroscopic dissection; histopathological evaluation.

RARE CASE OF BRAIN METASTASIS FROM PROSTATE CARCINOMA: HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL FINDINGS

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Objective: This case report aimed to present a rare instance of brain metastasis from a mixed ductal and acinar prostate carcinoma, highlighting the histopathological features and immunohistochemical profile.
Case Report: A histopathological analysis was performed on a lobulated tissue fragment measuring 4.5 x 3.5 x 3 cm, which included a portion of the cerebral cortex with a 3 cm lesion. Microscopic examination revealed a cystic change, approximately 1.2 cm in diameter, filled with blood, surrounded by a whitish soft neoplastic tissue. The neoplasm consisted of malignant cells arranged in solid nests with cribriform and papillary patterns, and the yellowish zone contained characteristic acinar formations. Emboli were found within small vascular spaces. Immunohistochemical analysis revealed that the malignant cells were positive for androgen receptors, with some cells also expressing prostate-specific antigen (PSA) and AMACR. Cytokeratins (CK7 and CK34βE12) were negative, while the proliferation index Ki-67 was positive in 25-40% of the cell population. Following diagnosis, a biopsy confirmed the presence of the neoplasm with a Gleason Score of 5+4.
Conclusion: This case underscores the importance of recognizing brain metastasis as a potential complication of prostate cancer, particularly in rare histological subtypes. The findings reinforce the need for thorough diagnostic evaluation and management of metastatic disease in patients with prostate carcinoma.

Keywords: brain metastasis, prostate cancer**,** immunohistochemistry.

RARE MESENCHYMAL TUMORS OF FEMALE GENITAL TRACT

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Introduction

Mesenchymal tumors of female genital tract arise from the smooth muscle, stroma, connective tissue, vascular, neural elements or others. The most common mesenchymal neoplasm is leiomyoma of the uterus. Malignant mesenchymal tumors of female genital tract are very rare neoplasms with aggressive behavior and often result in local recurrence and distant metastases. Apart from endometrial stromal sarcoma and leiomyosarcoma, there are highly aggressive neoplasms with unknown pathogenesis, or associated with inherited syndromes, refractory to systemic chemotherapy or radiation therapy. Their diagnosis is challenging due to their rarity and overlapping features with other tumors. We present 4 cases of rare mesenchymal tumors that posed serious diagnostic challenge.

Case 1. 46-year-old female with hysterectomy, with tumor on the anterior uterine wall with dimensions 5x5x4,5 cm, well circumscribed, grayish, with numerous vascular spaces filled with blood and areas of hemorrhage. The histological analyses showed morphology of vascular lipoleiomyoma, a rare benign tumor, with estimated incidence 0,06% of benign uterine lesions, first described in 1964. The tumor has unknown pathogenesis, and should be distinguished from PEComa by immunohistochemical staining with HMB45.

Case 2. 35-year-old female patient with myomectomy of two tumor nodes with dimensions 7x5,5x5 cm and 4,5x2,5x2 cm, showing similar gross appearance. The larger node was composed of spindle cells with focal moderate to severe nuclear atypia, staghorn blood vessels, 3 mitoses per 10 high power fields. The immunohistochemical analysis confirmed absence of fumarate hydratase in neoplastic cells of the larger node, unlike the cells in the smaller node, which showed positive signal. Fumarate hydratase deficient leiomyoma is a rare entity with prevalence of 0,4-1,6% of all uterine leiomyomas, appearing at younger age in comparison to conventional leiomyomas. A small percentage of these tumors are linked to hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, which involves germline *FH* mutations, and the potential hereditary implications should initiate patient counseling and surveillance of associated cancer risks.

Case 3. 66-year-old female patient with tumorectomy of vaginal tumor. Approximately 30 fragments of soft tissue tumor with dimensions of 0,2 cm to 5x3,5x2,5 cm, with grayish-white to yellow color were submitted for histopathological analyses. The microscopic analysis showed highly cellular tumor composed of bland spindle cells, positive for CD117, CD34, DOG1 and mitotic index of 17 mitoses per 10 high power fields. The gastroscopy and colonoscopy did not show evidence of tumors. Extragastrointestinal stromal tumor (EGISTs) are rare tumors, representing 5-15% of all GISTs, and the vagina is an extremely rare extragastrointestinal localization, with estimated prevalence of 1%. Secondary deposits from primary GIST should be excluded.

Case 4. 19-year-old female patient with biopsy due to tumor of vagina. The analyses showed undifferentiated small round cell sarcoma composed of monomorphic small round cells with dominant nuclei, and multiple areas of necrosis. The cells were positive for CD99, CD56, ERG, WT1 and retained INI1 expression. The subsequent imaging analyses showed large tumor in the pelvis, enlarged pelvic lymph nodes and multiple metastatic deposits in lungs, pleura, bones. The molecular analyses were negative for predictive gene mutations.

Conclusion

Rare mesenchymal tumors of the female genital tract require careful pathological evaluation for accurate diagnosis, as well as awareness of their clinical, imaging and laboratory data. Multidisciplinary approach is essential for the diagnosis and treatment.

Keywords: mesenchymal tumor, female genital tract.

MESONEPHRIC-LIKE ADENOCARCINOMA OF THE UTERUS

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Introduction: Mesonephric-like adenocarcinoma (MLA) of the uterus is an uncommon and recently characterized subtype of endometrial carcinoma. It exhibits morphologic and molecular similarities to mesonephric adenocarcinoma of the cervix but arises in the endometrium. Owing to its rarity and histologic diversity, MLA is frequently underrecognized, which may affect patient management given its potentially aggressive behaviour.
Case Presentation: We describe two rare cases of uterine mesonephric-like adenocarcinoma and carcinosarcoma in postmenopausal women who presented with abnormal uterine bleeding. Radiologic evaluation revealed endometrial-based masses confined to the uterus at diagnosis. Histologic examination showed heterogeneous growth patterns, including tubular, glandular, and solid architectures, with characteristic eosinophilic intraluminal secretions. Immunohistochemical analysis demonstrated diffuse expression of PAX8 and GATA3, focal TTF-1 positivity, and absence of estrogen and progesterone receptor expression, supporting the diagnosis of MLA. Targeted molecular analysis revealed activating KRAS mutations in both tumors. Both patients underwent total hysterectomy with bilateral salpingo-oophorectomy.
Conclusion: Uterine mesonephric-like adenocarcinoma is a rare but clinically significant entity with distinctive pathologic features and a potential for aggressive behaviour. Reporting additional cases is crucial to improve diagnostic accuracy and optimize management strategies.

Keywords: mesonephric-like adenocarcinoma, uterus, endometrial carcinoma, immunohistochemistry, KRAS mutation.

SURVIVAL OF ADVANCED STAGE HIGH-GRADE SEROUS OVARIAN CANCER PATIENTS: CHALLENGES FOR THE FUTURE

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Background: High-grade serous ovarian cancer (HGSOC) is the most lethal gynecologic malignancy, with over 70% of cases diagnosed at advanced stages. Despite therapeutic advances, overall survival remains poor due to widespread peritoneal dissemination, chemoresistance, and molecular heterogeneity.
Methods: We synthesized recent evidence from SEER (2015–2023), phase III trials (SOLO-1, PAOLA-1, PRIMA, ATHENA-MONO, MIRASOL), and guideline updates (NCCN v3.2025; ESGO–ESMO–ESP consensus). Long-term outcomes from OVHIPEC-1 and real-world datasets were included. Molecular pathology perspectives incorporated homologous recombination deficiency (HRD) assays, BRCA testing, FRα immunohistochemistry, and CCNE1 amplification.
Results: Five-year relative survival for ovarian cancer improved to 55.1% in 2022, yet distant-stage survival remains only 31.8%. Cytoreductive surgery aiming for no residual disease remains a key determinant of survival, with HIPEC at interval debulking demonstrating a durable overall survival advantage in selected stage III patients.
Maintenance therapy with PARP inhibitors demonstrates the greatest benefit in BRCA-mutated and HRD-positive tumors, while bevacizumab provides modest benefit, particularly in high-risk and biologically defined subgroups. Mirvetuximab soravtansine has established itself as a new standard of care in platinum-resistant, FRα-high disease, significantly improving survival and quality of life.
From a pathology standpoint, precise molecular reporting is essential: HRD/BRCA testing guides PARP eligibility, FRα IHC is required for ADC therapy, and CCNE1 amplification identifies tumors unlikely to benefit from PARP. Standardization of HRD assays and integration of molecular diagnostics into multidisciplinary tumor boards are ongoing challenges.
Conclusion: Advanced-stage HGSOC management requires close collaboration between gynecologic oncologists and pathologists. High-quality cytoreduction, biomarker-driven systemic therapy, and integration of emerging strategies such as ADCs, targeted inhibitors for HRP/CCNE1 tumors, and digital pathology represent critical steps forward. Equitable access to surgery, testing, and innovative treatments remains a pressing challenge to achieve broader survival gains.

Keywords: high-grade serous carcinoma, molecular testing, personalized treatment.

VAGINAL MICROBIOME AND HPV INTERPLAY

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The vaginal microbiome is a dynamic ecosystem that maintains a balance between protective *Lactobacillus species* and potentially pathogenic microorganisms, thereby playing a crucial role in vaginal health. Emerging evidence suggests that the composition of the vaginal microbiome influences the acquisition, persistence, and pathogenicity of human papillomavirus (HPV), as well as the development and progression of cervical intraepithelial lesions. *Lactobacilli* contribute to vaginal homeostasis through lactic acid production, which lowers vaginal pH, enhances the antimicrobial activity of hydrogen peroxide and bacteriocins, and inhibits opportunistic infections, including HPV. The D-lactic acid isomer further increases cervicovaginal mucus viscosity, providing additional protection against urogenital infections and facilitating the degradation of HPV viral particles.

An increased abundance of strict anaerobes associated with bacterial vaginosis has been frequently observed in women with cervical dysplasia. These microorganisms may compromise the epithelial barrier through enzymatic activity, thereby facilitating HPV entry. In HPV-positive women with cervical intraepithelial lesions, *Lactobacillus iners* often predominates, although its functional role remains controversial. A vaginal pH greater than 5 is associated with a 10–20% increased risk of HPV positivity in premenopausal women, possibly due to the sensitivity of the HPV E5 oncoprotein to acidic conditions.

Despite reported associations between HPV infection, vaginal dysbiosis, and cervical pathology, existing data remain inconsistent due to diagnostic limitations and the heterogeneous nature of bacterial vaginosis. Further research is required to elucidate the complex interactions between host factors, vaginal microbiota, and cervical carcinogenesis. Clarifying these relationships may enable the development of microbiome-targeted preventive and therapeutic strategies.

Keywords: Human papillomavirus, vaginal microbiome, dysbiosis

MOLECULAR CLASSIFICATION OF ENDOMETRIAL CARCINOMA (EC)

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TCGA performed an integrating genomic, transcriptomic and proteomic characterization of EC, identifying four groups of tumors: Group 1, with somatic inactivating mutations in the POLE exonuclease and very high mutation rates (ultramutated) (7%), associated with a good prognosis. These tumors exhibited a mutation profile characterized by mutations in PTEN (94%), PIK3CA (71%), PIK3R1 (65%), FBXW7 (82%), ARID1A (76%), KRAS (53%), and ARID5B (47%); Group 2 included EEC with microsatellite instability (MSI/MMRD) (hypermutated), and high mutation rates (28%), associated with intermediate prognosis. These tumors showed a high mutation rate, and mutations in PTEN (88%), RPL22 (33%), KRAS (35%), PIK3CA (54%), PIK3R1 (40%), and ARID1A (37%); Group 3 tumors included EEC with low copy-number alterations, also referred to as tumors with a nonspecific molecular profile (NSMP) (39%), associated with intermediate prognosis. They showed a low mutation rate, and mutations in PTEN (77%), CTNNB1 (52%), PIK3CA (53%), PIK3R1 (33%), and ARID1A (42%); Group 4 (serous-like or copy-number high) (26%) showed a low mutation rate, but frequent mutations in TP53 (92%), PPP2R1A (22%) and PIK3CA (47%), and were associated with worse prognosis. They exhibited chromosomal instability, and recurrent amplifications (MYC, ERBB2, CCNE1, FGFR3, SOX17).

Different groups have proposed a surrogate, composed of three immunohistochemical markers (p53, MSH6 and PMS2) and one molecular test (mutation analysis of POLE), as an approach to bring the molecular classification into clinical practice. Several studies have demonstrated the prognostic value of this surrogate approach. Interestingly, some EC appear to be double classifiers according to TCGA classification. Since the TCGA publication, several international guidelines have incorporated the molecular classification in risk stratification. The ESGO-ESTRO-ESP guidelines were the first that introduced molecular subtypes as key elements in risk stratification together with conventional pathologic features. Very recently FIGO staging system has been updated, incorporating several pathological features (myometrial invasion, cervical stromal invasion, lymphovascular space invasion and histologic typing) together with molecular classification (POLE mutated, and p53 abnormal) in staging. The TCGA surrogate approach has been shown to be particularly helpful in the group of grade 3 endometrioid carcinomas (EEC3). The vast majority of low grade endometrioid carcinomas (EEC) are NSMP or MSI/MMRD, with POLE-mutated, or TP53-abnormal tumors accounting for less than 10%. Moreover, the vast majority (95%) of SC are TP53 abnormal. New scientific evidence has been produced in this field, since the initial publication of TCGA. The new scientific evidence shows that the four molecular subtypes are not homogeneous groups of tumors, but composed of several subsets. Accumulated data has confirmed the good prognosis of patients with POLE-mutant tumors. An important advance in this field was the recognition that POLE mutations can be classified as pathogenic (associated with good prognosis) and non-pathogenic. Well recognized pathogenic mutations are: P286R, V411L, S297F, S459F, A456P, F367S, L424I, M295R, P436R, M444K, D368Y. They are usually clonal, associated with high mutation load, generation of numerous neo-antigens, and good prognosis. In contrast, non-pathogenic POLE mutations, are usually subclonal, sometimes secondary to mismatch repair deficiency, and not associated with high mutation load. Although pathogenic POLE mutations are associated with good prognosis, cumulative data has shown that around 9% of patients with pathogenic POLE mutations are found at advanced stage (FIGO III/IV), around 4% show

progression of the disease (30% of those at advanced stages) and 1% die of the disease. The MSI/MMRD group is also heterogeneous, particularly after analysis of successful clinical trials with immune checkpoint inhibitors. The group of tumors with non-specific molecular profile is also heterogeneous. In recent years, the focus has been put on new biomarkers - L1CAM expression or CTNNB1 mutations. However, recent studies show that high histologic grade and negativity to estrogen receptor expression could be two important findings to identify patients with worse prognosis. Finally, the group of TP53 abnormal tumors is also heterogeneous, with different histologic subtypes (EEC3, serous carcinomas and carcinosarcomas) with different pattern of tumor spread. However, overall survival is similar, regardless of the histologic type.

Keywords: endometrial cancer, molecular classification, survival.

INTEGRATING MOLECULAR FEATURES IN PATHOLOGY OF OVARIAN CANCER

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Ovarian cancer is a heterogeneous disease, with five main histologic types:
High-grade serous carcinoma (HGOSC) is the most common type (70%). It usually presents in advanced stage. The cell of origin is located in the epithelium of the fallopian tubes (tubal serous intraepithelial carcinoma, STIC) in a significant proportion of cases. Microscopically, they show papillary or solid architecture, with marked cellular pleomorphism. Tumor cells are positive for WT1, PAX8 and frequently for estrogen receptors. They usually have aberrant expression of p53 (mutated pattern), and a TP53 mutation. About 50% have homologous recombination deficiency, and 25% have germline and somatic mutations of the BRCA genes. They are microscopically and molecularly indistinguishable from serous carcinomas of the fallopian tube and peritoneum. Sometimes the tumor affects these three locations, and specific criteria are used to determine the origin, which is in the fallopian tube in most cases.
Low-grade serous carcinoma is infrequent (5%), and occasionally originates in a borderline serous tumor. It shows a papillary architecture, and the cells have little pleomorphism. Tumor cells usually express WT-1 and estrogen receptors, but have a wild-type pattern of p53 expression, which is consistent with the absence of mutations in this gene. They have a low mitotic index and low positivity for Ki67. They do not usually have homologous recombination deficiency or mutations in BRCA1/2. Very rarely, they transform into high-grade anaplastic carcinomas, which are microscopically and molecularly different from high-grade serous carcinomas.
Endometrioid carcinomas represent 10% of ovarian cancers. They are identical to endometrioid carcinomas of the endometrium, and are occasionally associated with endometriosis. The majority are low-grade tumors (grade 1 and 2), although up to 30% can be high-grade. High-grade carcinomas may have homologous recombination deficiency, but less frequently than high-grade serous carcinomas. From a molecular point of view, they have PTEN or CTNNB1 mutations (especially in low-grade ones), and can be classified molecularly in a similar way to endometrial cancers in four groups.
Clear cell carcinomas account for 10% of ovarian cancers. They are identical to clear cell carcinomas of the endometrium, and are occasionally associated with endometriosis. They are considered high-grade carcinomas. They usually have clear cells, but also polygonal or hobnail cells. The architectural pattern is characteristically composed of a solid and a tubulo-papillary arrangement. They can also be classified molecularly in a similar way to endometrioid carcinomas, although most of them have a non-specific molecular profile. They do not usually have homologous recombination deficiency, nor mutations in BRCA1/2. They frequently have mutations in ARID1A.
Mucinous carcinoma account for 5% of ovarian cancers. It must be distinguished from ovarian metastases originating from mucinous carcinomas of the digestive tract or endocervix. They tend to be very large and very frequently coexist with areas of mucinous cystadenoma or borderline mucinous tumor. The architectural pattern (invasive or expansive) has prognostic significance. They usually have mutations in K-RAS, and some cases may exhibit TP53 mutations, or HER-2 amplification. They do not usually have homologous recombination deficiency or BRCA1/2 mutations.
Advances in molecular pathology of HGOSC have shown that approximately 50% of tumors are deficient in homologous recombination (HRD), one of the mechanisms of cell DNA repair.

These tumors respond better to platinum-based therapies and PARP inhibition and are associated with improved prognosis. HRD is caused by alterations in genes in the homologous recombination pathway, including BRCA-1 and 2. Nowadays, a genomic Instability test (GI) is the best method to identify HRD. Based on results of prospective clinical trials with PARP inhibitors, ESMO guidelines recommended two GI tests, Myriad MyChoice, and Foundation, both of which are based on identification loss of heterozygosity (LOH) along the genome, and large-state scale transitions and telomeric imbalance (Myriad). Due to limitations of the two validated tests, different commercial companies and academic groups have developed alternative tests that are in the process of being validated at analytical and clinical levels. The use of Myriad MyChoice, Foundation and the new tests for HRD, allows also a better characterization of the group of tumors that do not have HRD. Ovarian HRP tumors have other specific driver gene alterations, such as CCNE1 amplification, Rb loss, NF1 loss, among others, but their contribution in sub-stratification has not been fully assessed. New biomarkers, such as HER2 and FR1α, may also play an important role in the decision of using specific treatments.

Keywords: ovarian cancer, histologic types, molecular markers.

PATHOLOGY OF ENDOMETRIAL CARCINOMA

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The most recent WHO classification defines different histologic types of endometrial carcinoma (EC), each with specific histological features, prognosis and molecular alterations.
Endometrioid carcinomas (EEC) account for 80% of all ECs, and exhibit a spectrum of morphologic features that includes tumors with mucinous differentiation, and high-grade tumors (EEC 3). The most frequent molecular alterations include microsatellite instability, and mutations in the PTEN, KRAS, PIK3CA, ARID1a and CTNNB1 genes. Approximately 30% of ECs show microsatellite instability (MSI)/ Mismatch repair deficiency (MMDR). About 3% of patients with EC are associated with hereditary nonpolyposis colon cancer (HNPCC; Lynch Syndrome), and about 27% are sporadic ECs with MSI/MMRD. It is generally accepted that IHC is the best test for detecting MSI/MMRD. PCR-based tests are important in cases when IHC is inconclusive. It is necessary to perform MLH-1 promoter methylation assays in all ECs with abnormal expression of MLH1. Several international guidelines recommend universal testing for MSI/MMRD for four reasons: 1) diagnostic value, as MSI/MMRD is considered a marker for EEC; 2) identification of patients with Lynch syndrome; 3) part of the surrogate to stratify patients according to TCGA-based molecular classification; and 4) prediction of potential utility of immune checkpoint inhibitor therapy. EEC have PTEN somatic mutations in 37-61% of cases, also detected in preneoplastic lesions. Patients with Cowden's syndrome, with inherited germline PTEN mutations have an increased risk of EC. KRAS mutations in EC range between 10 and 30%, and FGFR2 mutations occur in 10–12% of EC, particularly in EEC (16%). FGFR2 mutations and KRAS mutations are mutually exclusive events. Mutations in PIK3CA occur in 23-39% of EC cases, frequently coexisting with mutations in PTEN. They have been associated with poor prognosis. Approximately 14% and 44% of ECs have CTNNB1 (beta-catenin gene) mutations. Their prognostic significance is controversial; but they tend to occur in tumors with favorable prognosis in general.
Serous carcinoma (SC) is invasive or restricted to the endometrial surface. Approximately 90% of SCs have TP53 mutations, which are also found in around 10-20% of EECs, particularly in EEC3. Immunohistochemical analysis of p53 constitutes a good surrogate for TP53 mutations. C-erbB2 overexpression and amplification are seen more frequently in SC (43%) than in EEC (29%).
Clear cell carcinoma (CCC) accounts for 2% of ECs, and has specific morphologic features. From a molecular point of view, CCC show TP53 mutations (39.7%), PIK3CA mutations (23.8%), and ARID1A mutations (15.9%), among others. A small subset of tumors shows MSI/MMRD (11.3%), and POLE mutations, which may be associated with improved prognosis.
Undifferentiated carcinomas show no degree of differentiation. MSI/MMRD is the predominant molecular feature, although TP53 mutations may also be found. POLE mutations have been detected in a few cases, and are associated with favorable prognosis. PI3K pathway mutations involving PTEN, PIK3CA or PIK3R1 are frequent (>50% of cases) as well as inactivating mutations in genes of the SWI/SNF complex proteins.
Mixed carcinomas are neoplasms composed of two or more different histological types, at least one of which is either serous or clear cell carcinoma.
Carcinosarcoma (CS) shows a microscopic appearance analogous to sarcomatoid or metaplastic carcinomas of other organs. According to TCGA, the genes more frequently

mutated in CS are TP53 (91%), FBXW7 (39%), PIK3CA (35%), PPP2R1A (28%), PTEN (19%), ARID1A (12%), and KRAS (12%), similar to SC and EEC. Regarding TCGA classification, most CSs belong to the copy-number high serous-like molecular subtype of EC, characterized by TP53 mutations and frequently accompanied by gene copy-number alterations, including amplification of CCNE1 and C-MYC. Approximately 20% of cases belong to the copy-number-low molecular subtype. Only few ECS belong to the MSI/MMRD molecular type and the POLE-mutated ultramutated molecular type. A typical feature of CS is the involvement of genes related to the epithelial-to-mesenchymal transition with a switch from E- to N-cadherin, downregulation of members of the miR-200 family.
Neuroendocrine carcinomas are very rare and display morphological characteristics of neuroendocrine differentiation.
Mesonephric-like carcinomas are aggressive tumors with frequent visceral metastasis. From the molecular viewpoint, they are characterized by KRAS mutations, but may also have mutations in NRAS, BRAF, PIK3CA, PTEN or CTNNB1.
Gastrointestinal type mucinous carcinoma is identical to its cervical counterpart and is occasionally associated with mutation-type p53 immunostaining.

Keywords: endometrial cancer, p53, histologic subtypes.

MODALITIES OF SURGICAL TREATMENT FOR CERVICAL INTRAEPITHELIAL NEOPLASIA

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Cervical intraepithelial neoplasia (CIN) represents a spectrum of premalignant lesions of the cervical epithelium with a well-established association with persistent high-risk human papillomavirus infection. Surgical treatment remains a cornerstone in the management of CIN, particularly for high-grade lesions, with the primary goals of eradicating disease, preventing progression to invasive cervical cancer, and preserving cervical function whenever possible. The choice of surgical modality depends on several factors, including the grade and extent of the lesion, transformation zone visibility, patient age, reproductive wishes, and local expertise. Excisional techniques, such as loop electrosurgical excision procedure (LEEP), cold knife conization, and laser conization, allow removal of the transformation zone with histopathological evaluation of margins and are generally preferred for CIN 2 and CIN 3. These methods provide high cure rates but may be associated with adverse obstetric outcomes, particularly when larger volumes of cervical tissue are removed. Ablative methods, including cryotherapy and laser ablation, destroy abnormal tissue *in situ* without specimen retrieval and are typically reserved for selected cases of low-grade or carefully evaluated high-grade CIN in which invasive disease has been reliably excluded.
Advances in surgical technology and better risk stratification have enabled more individualized treatment approaches, balancing oncologic safety with fertility preservation. Post-treatment surveillance using cytology and high-risk HPV testing is essential to detect residual or recurrent disease. Overall, surgical management of CIN is highly effective, but optimal outcomes require appropriate patient selection, adherence to evidence-based guidelines, and integration of preventive strategies such as HPV vaccination and screening.

Keywords: cervical intraepithelial neoplasia, excisional techniques, high-risk HPV testing.

PATHOLOGY AND CLASSIFICATION OF CERVICAL CANCER

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The WHO Classification of Female Genital Tumors is the fourth volume in the fifth edition of the WHO series on the classification of human tumors, and was fundamentally revised in 2020 due to new histomorphological data and, in particular, molecular pathology data.
It does not take into account the depth of invasion or the relationship of the tumor to the large vessels in cervical stroma.

- The 5th WHO classification of FGT* is now primarily constructed on the basis of new (molecular) pathology data; and with obligation to use the diagnostic histopathological standards and terminology according to the current WHO classification.
- The new WHO classification differentiates between HPV-associated and HPV-independent squamous cell carcinoma due to their different pathogenesis.
- The previous diagnostic category of **AC-NOS** no longer exists in the new edition of the WHO classification.
- SMILE (stratified mucin-producing intraepithelial lesion) as a subtype of AIS is no longer listed as an independent entity.
- Morphological evaluation helps us decide the further workup of any lesion or tumor and supports the selection of immunostains as next step in the process of establishing diagnosis.
- The so-called **Silva pattern**, a prognostically relevant classification of (HPV-associated) AC based on architectural criteria, has been newly adopted into the WHO classification.
- Diffuse moderate to strong p16 staining serves as a surrogate marker for high-risk HPV associated cervical adenocarcinoma.
- Immunohistochemistry reveals more than a standard biopsy test. It enables pathologists to determine the exact type and subtype of cancer by looking for unique tumor markers within cancer cells.

Keywords: cervical cancer, classification, immunohistochemistry.

PATHOLOGY OF INFLAMMATORY SKIN LESIONS

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Inflammatory skin lesions represent a broad and complex category of dermatologic conditions, often posing significant diagnostic challenges to both clinicians and pathologists.
Histopathological examination remains a cornerstone in the evaluation of these lesions, yet many inflammatory dermatoses exhibit overlapping or nonspecific microscopic features. Key diagnostic patterns - such as spongiotic, lichenoid, interface, psoriasiform, and granulomatous reactions - can be seen across a range of clinical entities, making reliance on histology alone insufficient. Moreover, changes induced by prior treatments, secondary infections, or lesion chronicity may further obscure definitive interpretation. As such, clinicopathological correlation is essential to reach an accurate diagnosis. Integrating clinical information - including lesion distribution, morphology, duration, symptoms, patient history, and response to prior treatments - with histological findings significantly enhances diagnostic precision. This collaborative approach allows for the differentiation between similar-appearing entities, such as distinguishing lupus erythematosus from dermatomyositis or drug eruptions from viral exanthems. Inadequate clinical information may lead to misdiagnosis, delayed treatment, or unnecessary interventions. Effective communication between dermatologists and pathologists, including detailed biopsy requisitions and discussion of differential diagnoses, is critical.
Ultimately, the accurate diagnosis of inflammatory skin disorders relies on a synergistic relationship between clinical assessment and histopathologic interpretation, underscoring the indispensable role of clinicopathological correlation in dermatopathology.

Keywords: inflammation, skin lesions, histopathology.

SURGICAL TREATMENT OF MELANOMA

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Surgical management is the primary treatment for cutaneous melanoma, focusing on complete tumor removal, accurate staging, and achieving optimal oncologic outcomes.
The standard approach for suspicious lesions is excisional biopsy with pathological examination to determine tumor type and thickness, guiding further treatment. Wide local excision is the cornerstone technique for melanoma, with margins based on Breslow thickness. Reconstructive options following melanoma excision vary depending on defect size and location, ranging from primary closure to skin grafts, local flaps, and free tissue transfer, to restore form and function while minimizing donor site morbidity.
Sentinel lymph node biopsy is recommended for intermediate to high-risk tumors, particularly those >1 mm thick or with ulceration, providing prognostic information and guiding adjuvant therapy. Therapeutic lymph node dissection is indicated for patients with clinically palpable or radiologically confirmed nodal metastases, aiming to achieve regional disease control and reduce tumor burden.
Although advancements in adjuvant and neoadjuvant therapies have impacted treatment practices, surgery remains crucial for early-stage melanoma, specific metastatic sites, and palliative care. Surgery plays a key role in obtaining a histological diagnosis and controlling local disease within the ever-evolving landscape of melanoma treatment.

Keywords: malignant melanoma, surgery, margins.

MELANOMA MALIGNUM -INOPERABLE DOESN'T MEANS INCURABLE

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In our study we present our management of advanced melanoma, emphasizing the integration of surgical, reconstructive, and systemic therapies. Below is a concise analysis of the key points and implications from the presented data:

Key Observations:

1. Patient Demographics and Lesion Distribution:
    - Cohort: 23 patients (12 male, 11 female); age 33–78 years, treated from January 2022 to March 2024.
    - Primary lesion locations: Trunk (52.1%), lower extremity (21.7%), upper extremity (17.4%), head and neck (8.6%).
    - This distribution aligns with typical melanoma patterns, with the trunk being the most common site, likely due to higher UV exposure in these areas.
2. Surgical Management:
    - All patients underwent wide local excision (WLE) of the primary lesion, the standard of care for localized melanoma.
    - Reconstructive techniques: Primary closure (n=16), split-thickness skin grafting (n=1), local flap coverage (n=6). The predominance of primary closure suggests most lesions were relatively small or in areas with sufficient tissue laxity.
    - Sentinel lymph node biopsy (SLNB) with technetium-99 radiotracer was used for staging, often followed by lymph node dissection, indicating adherence to guidelines for accurate nodal assessment.
3. Advanced Disease and Systemic Therapy:
    - Eight patients developed inoperable metastatic disease, historically associated with poor prognosis and palliative care.
    - Systemic therapies included:
        - Immune checkpoint inhibitors (ICIs): Anti–PD-1 and anti–CTLA-4 therapies were used in all 8 patients, reflecting their established role in advanced melanoma.
        - Targeted therapy: Six patients with BRAF mutations received BRAF/MEK inhibitors, consistent with precision medicine approaches for BRAF-mutant melanoma (approximately 40–50% of cases).
    - Outcomes: Measurable disease regression in 6 patients and durable remission in 3, with a median follow-up of 18 months. These results highlight the transformative impact of ICIs and targeted therapies, with response rates aligning with clinical trial data (e.g., ~40–60% response rates for ICI combinations and ~70% for BRAF/MEK inhibitors).
4. Clinical Implications:
    - The shift from palliative care to active treatment in inoperable melanoma underscores the efficacy of modern systemic therapies.
    - Multidisciplinary care, combining surgical expertise, precise staging (via SLNB), and tailored systemic treatments, is critical for optimizing outcomes.
    - The data supports the notion that advanced melanoma, even when inoperable, is increasingly manageable, with potential for prolonged survival and remission.

Additional Considerations:

- Staging and Prognosis: The use of SLNB with technetium-99 ensured accurate staging, which is crucial for guiding adjuvant or systemic therapy decisions. The series does not specify AJCC staging, but inoperable metastatic disease suggests stage IV or high-risk stage III.
- Therapeutic Advances: The success of ICIs (e.g., nivolumab, pembrolizumab, ipilimumab) and BRAF/MEK inhibitors (e.g., dabrafenib/trametinib) reflects their established efficacy. However, the series does not mention adverse events, which can be significant (e.g., immune-related toxicities or resistance to targeted therapy).
- Follow-Up: The 18-month median follow-up is relatively short for assessing long-term survival, particularly for durable remission. Longer-term data would clarify the sustainability of these responses.
- Reconstruction: The use of local flaps and STSG in a minority of cases suggests complex defects in some patients, potentially impacting quality of life and functional outcomes.

Visual Representation (Chart):

To illustrate the distribution of primary lesion locations, a pie chart is provided below:

Grok can make mistakes. Always check original sources.

Conclusion:

This case series demonstrates that advanced melanoma, even when inoperable, is no longer synonymous with incurability. The combination of meticulous surgical staging, reconstructive techniques, and modern systemic therapies (ICIs and BRAF/MEK inhibitors) has significantly improved outcomes. Multidisciplinary care remains essential, and further studies with longer follow-up are needed to assess the durability of these responses and optimize treatment algorithms.

Keywords: malignant melanoma, personalized therapy, inoperable.

THERAPEUTIC OPTIONS IN ADVANCED MELANOMA

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Advanced melanoma, once considered a disease with dismal prognosis, was historically managed with surgery, radiotherapy, and chemotherapy. These approaches offered limited benefit, with short-lived responses and minimal impact on long-term survival.
The advent of modern systemic therapies has dramatically changed outcomes. Immune checkpoint inhibitors targeting PD-1, CTLA-4, and more recently LAG-3, have achieved durable responses and significantly improved survival, with long-term remission possible in a substantial subset of patients. Precision oncology has further expanded treatment options through targeted therapy against BRAF mutations, as well as selected benefit in KIT and NRAS alterations. Emerging modalities, such as tumor-infiltrating lymphocyte therapy, oncolytic viruses, and therapeutic vaccines, are under active investigation and hold promise for the future.
This presentation provides an overview of current therapeutic strategies for advanced melanoma, emphasizing the evolution from limited and palliative options to a new era of personalized and effective treatments.

Keywords: malignant melanoma, therapy, personalized medicine.

PROSTATE CARCINOMA *VERSUS* ATYPICAL SMALL ACINAR PROLIFERATION: DIAGNOSTIC CHALLENGES PRESENTED THROUGH A CASE REPORT

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Objective: The definitive diagnosis of prostate cancer (PCa) relies on histopathological examination of prostate core needle biopsies. While the presence of malignant cells is often unequivocal, a subset of biopsies yields findings of atypical small acinar proliferation (ASAP) that are neither definitively benign nor malignant. This diagnostic uncertainty presents a significant challenge for pathologists and clinicians, with critical implications for patient management. This case report highlights the diagnostic challenges of differentiating ASAP from PCa and illustrates the subsequent patient management pathway.
Material and Methods: A transrectal ultrasound-guided (TRUS) 12-core prostate biopsy was performed, and samples were obtained from designated areas.
Immunohistochemical analyses with AMACR and CK34betaE12 were performed on all submitted samples.
Results: Microscopic examination on L4 samples revealed glandular focus measuring less than 1 mm, containing 3-4 glands with morphological features of ASAP.
Immunohistochemistry of the epithelium revealed marked positive expression for AMACR, and no expression for CK34betaE12.
Conclusion: The diagnosis of ASAP on a prostate biopsy is a significant finding that demands a systematic approach to patient management. This case report illustrates the diagnostic uncertainty and the pathway from an ASAP diagnosis to a definitive diagnosis of prostate cancer. An accurate diagnosis using multi-modal approach is crucial for avoiding both the over-treatment of a benign process and the under-treatment of a potential malignancy.

Keywords: Prostate carcinoma, ASAP, TRUS.

MORPHOLOGICAL PREDICTORS IN GRADE GROUP 2 PROSTATE CANCER: THE ROLE OF GLEASON 4 QUANTIFICATION

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Introduction: Grade Group 2 prostate adenocarcinoma, defined as Gleason score 7 (3+4), is heterogeneous, with variable prognosis. The proportion of Gleason pattern 4 (GP4) is a key factor, but its predictive value remains unclear in TRUS-biopsy cohorts without MRI.
Aim: To evaluate the prognostic role of GP4 proportion and other morphological parameters in Grade Group 2 prostate cancer.
Materials and Methods: A retrospective series of 100 patients (2020–2025) with Gleason score 7 (3+4) prostate adenocarcinoma was analyzed. Biopsies were stratified into ≤25% (n=72) and >25% (n=28) GP4 groups. Parameters included tumor %, positive cores, bilaterality, extent, and perineural invasion (PNI). A morphological score (0–7) categorized cases as favorable (0–2), intermediate (3–4), or unfavorable (5–7). Logistic regression identified predictors of unfavorable risk.
Results: In the ≤25% GP4 group, 51% were favorable, 32% intermediate, and 17% unfavorable. In the >25% GP4 group, 7% were favorable, 54% intermediate and 39% unfavorable. Wilcoxon and Fisher confirmed association between GP4 and risk ($p<0.0001$), but not PNI ($p=0.655$). Logistic regression showed GP4 (OR=1.22, $p=0.014$) and tumor % (OR=1.30, $p=0.003$) as independent predictors, while PNI showed a nonsignificant trend (OR≈6.08, $p=0.12$).
Conclusion: GP4 quantification is an essential prognostic parameter in Grade Group 2 prostate cancer. Both GP4 and tumor percentage independently predict unfavorable risk, supporting inclusion of these measures in routine pathology reports, particularly in settings without advanced imaging.

Keywords: Gleason pattern 4; Grade Group 2; prostate cancer; morphological predictors; risk stratification.

PROSTATE MRI AND PI-RADS: IMAGING MEETS PATHOLOGY

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Introduction: Multiparametric magnetic resonance imaging (mpMRI) has revolutionized the diagnostic approach to prostate cancer, providing detailed anatomical and functional insights that complement clinical and histopathologic data. The introduction and refinement of the Prostate Imaging–Reporting and Data System (PI-RADS) have brought standardization to prostate MRI interpretation, improving communication among radiologists, urologists, and pathologists.
Material and methods: We present the evolving role of mpMRI in the detection, localization, and staging of clinically significant prostate cancer, emphasizing the integration of PI-RADS with histopathological outcomes.
Results: Through case-based discussions in the hospital Acibadem Sistina, we examined how PI-RADS scores correlated with biopsy and prostatectomy specimens, highlighting both strengths and limitations of imaging in real-world practice. The focus of interest was the anatomical basis of lesion localization, the interpretation of diffusion-weighted and dynamic contrast-enhanced imaging, and the differentiation between indolent and aggressive disease. Common diagnostic pitfalls were also addressed, including false positives in the transition zone and post-biopsy changes by fostering a better understanding of the radiologic-pathologic correlation, in order to enhance interdisciplinary collaboration and promote more accurate, patient-centered decision-making.
Conclusion: This presentation is intended for radiologists, urologists, pathologists, and trainees involved in prostate cancer diagnosis and management in order to give practical insights into optimizing MRI protocols, interpreting PI-RADS with confidence, and appreciating how imaging findings translate into histologic truth.

Keywords: multiparametric magnetic resonance imaging, Prostate Imaging–Reporting and Data System, radiologists, pathologists.

RARE AND INTRIGUING CASE OF PRIMARY EPITHELOID ANGIOSARCOMA OF THE VULVA

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Epithelioid angiosarcoma of the vulva is an exceptionally rare and highly aggressive vascular malignancy with uncertain etiology, though risk factors such as prior radiotherapy and chronic lymphedema have been identified.
We report the case of a 44-year-old woman with no significant medical history who presented with a rapidly enlarging, foul-smelling mass on the right labia majora. The tumor measured 30 cm and exhibited central necrosis, ulceration, and bleeding. Radical tumor resection and right inguinal lymphadenectomy were performed, followed by reconstruction using a keystone design perforator island flap and a V-Y advancement flap. Microscopy revealed a malignant mesenchymal neoplasm comprising polygonal to spindle-shaped cells with eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli, with areas of solid, diffuse growth and focal vascular channel formation. Immunohistochemical analysis confirmed vascular endothelial differentiation (ERG+, CD31+, CD34+, Podoplanin+, EMA+) while excluding other mesenchymal tumors (SMA-, Desmin-, S-100-, CD68-, AE1/AE3-, HHV-8-). Ki-67 proliferation index of 60% indicated high proliferative activity. Further treatment consisted of adjuvant radiotherapy (61 Gy) and doxorubicin-based chemotherapy. At one-year follow-up, the patient remained free of recurrence or metastasis.
Primary epithelioid angiosarcoma of the vulva is extremely rare and the diagnosis is challenging requiring comprehensive immunohistochemical characterization for accurate diagnosis. Management involves radical surgical resection with adjuvant radiotherapy and chemotherapy as indicated, while detailed knowledge of pathological features and standardized immunohistochemical evaluation remains critical. Reporting such cases is essential to enhance understanding and guide evidence-based management of these challenging neoplasms.

Keywords: primary epitheloid angiosarcoma; vulvar angiosarcoma; gynecologic malignancy; rare tumor.

NEUROPATHOLOGY ADVANCEMENTS IN BRAIN TUMOR DIAGNOSTICS: EXPERIENCE FROM THE INSTITUTE OF PATHOLOGY – UKIM

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Background: Neuropathology has become an essential pillar of brain tumor diagnostics at the Institute of Pathology, Ss. Cyril and Methodius University in Skopje, N. Macedonia. The integration of histopathology, immunohistochemistry (IHC), and molecular profiling has strengthened diagnostic precision. With the introduction of next-generation sequencing (NGS), the Institute is continuously incorporating the 2021 WHO Classification of central nervous system tumors into routine practice.
Objective: To highlight the institutional experience in applying integrated diagnostic approaches for high-grade gliomas.
Methods: Adult patients with histologically defined high-grade astrocytic tumors were analyzed. Conventional morphology was complemented by IHC markers, such as IDH1/2, OLIG2, ATRX, H3K27me3 and MGMT. For diagnostically uncertain cases, multiplex ligation–dependent probe amplification (MLPA) was applied. Clinical and therapeutic data were included for correlation with outcomes.
Results: IHC and molecular testing enabled clear separation of IDH-mutant astrocytomas from IDH-wildtype glioblastomas. The diagnostic reliability of IHC was reinforced through strong concordance with molecular analyses. Patients with IDH-mutant astrocytomas demonstrated longer survival compared to glioblastoma IDH-wildtype cases, consistent with international observations. MGMT promoter methylation provided further stratification regarding treatment response and prognosis.
Conclusion: The Institute's experience confirms that combining morphological, immunohistochemical, and molecular tools advances accurate classification and prognostication of CNS tumors. Implementation of NGS ensures alignment with global standards, strengthens precision oncology, and underscores the role of the Institute of Pathology as a national reference center for neuropathological diagnostics and translational practice.

Keywords: neuropathology, high-grade glioma, WHO, molecular diagnostics, NGS.

ANGIOSARCOMA OF THE GALLBLADDER: A RARE CASE REPORT

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Introduction: Angiosarcoma of the gallbladder is an extremely rare, aggressive malignant neoplasm with a poor prognosis. With only 13 reported cases in the literature, it presents a challenge for diagnosis regarding clinical presentation. The symptoms mimic benign conditions like acute cholecystitis, and a long history of gallstones is a known risk factor. Imaging, such as CT scans, is essential, but a definitive diagnosis is made with pathological examination of the gallbladder tissue after surgery. Surgical resection is the main treatment when the tumor is localized and can be removed.
Case report: We present the case of a 72-year-old female patient with symptoms of epigastric pain and right hypochondrium for 3 months, with a known history of cholelithiasis. CT revealed an unexplained mass in the gallbladder. The cholecystectomy with regional lymphadenectomy was performed, and the gallbladder measured 8x6x4.5 cm, with a transmural tumor mass 4.5x3.5x3cm perforating the serosal surface. The lesion histology showed a malignant neoplasm with the morphology of epithelioid angiosarcoma. Immunohistochemistry demonstrated the following profile: CD31(+), CD34(+), ERG(+), CKAE1/AE3(-), CK7(-), S-100(-), SMA(-). According to the WHO Classification of Digestive System Tumors, staging of angiosarcoma is not recommended due to its biologic behavior, and it is not consistent with the staging system for soft tissue tumors.
Conclusion: Histological and immunohistochemical analyses play a major role in the diagnosis of gallbladder angiosarcoma. Preventive cholecystectomy is recommended in long-standing cholelithiasis. More comprehensive clinical studies are required to provide universal guidelines for the treatment and diagnosis of angiosarcoma of the gallbladder.

Keywords: angiosarcoma, gallbladder, gallstones.

SENTINEL LYMPH NODE BIOPSY FOR MALIGNANT MELANOMA

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Background: Sentinel lymph node biopsy (SLNB) is a minimally invasive procedure to identify and examine the first lymph node(s) receiving drainage from a primary tumor. SLNB represents the gold standard for staging clinically node-negative melanoma, guiding management of intermediate-thickness and high-risk lesions.
Methods: We retrospectively evaluated 85 consecutive patients who underwent SLNB for cutaneous melanoma between 2010 and 2025, analyzing demographics, tumor primary site, Breslow thickness, sentinel node basin distribution and lymphatic mapping patterns.
Results: The cohort comprised 85 patients with a mean age of 53.9 years (range 23-87). Primary tumor distribution was: trunk 37 (43.5%), lower extremities 34 (40.0%), upper extremities 11 (12.9%), and head/neck 2 (2.4%). The back (28.2%) and lower leg (23.5%) were most common subsites. SLNB was performed in the axilla (47.1%, including 3 bilateral), inguinal region (41.2%), and neck (2.4%). Three patients (3.5%) had positive in-transit nodes. Overall, SLNB was positive in 25.9% of patients. SLNB positivity correlated with increasing tumor depth: 10% of tumors 1.01–2.0 mm, 22.2% of tumors 2.01–4.0 mm, and 36.4% of tumors >4.0 mm. Almost all positive cases exhibited ulceration.
Conclusion: Lymphatic drainage followed predictable patterns: trunk and upper-extremity melanomas drained to axillary basins, lower-extremity lesions to inguinal nodes, and head/neck tumors to cervical basins. SLNB positivity was closely associated with increasing Breslow thickness and ulceration presence. SLNB status remains the paramount predictor of recurrence and survival, directing adjuvant therapy in the immunotherapy era. Ongoing analysis will refine risk stratification and optimize melanoma care.

Keywords: sentinel lymph node biopsy, melanoma staging, Breslow thickness, lymphatic mapping.

RARE BENIGN MELANOCYTIC LESIONS – REPORT OF TWO CASES

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Introduction: Rare benign melanocytic lesions can pose significant diagnostic challenges, especially when mimicking malignant melanoma both clinically and histologically. We present two unusual cases highlighting the importance of integrating histology and immunohistochemistry in establishing accurate diagnoses.
Case 1: A 37-year-old female presented with a slowly enlarging pigmented nodule on the foot. Histological evaluation revealed heavily pigmented epithelioid and spindle-shaped melanocytes arranged in nests and sheets, with low mitotic activity. Immunohistochemistry (IHC) showed strong positivity for Melan-A, HMB-45, and S-100, while Ki-67 proliferation index was low, supporting the diagnosis of pigmented epithelioid melanocytoma.
Case 2: A 25-year-old male presented with a pigmented lesion on the buttocks. Histology demonstrated a deeply located, wedge-shaped proliferation of dendritic melanocytes with prominent pigmentation extending into the deep dermis. IHC showed diffuse S-100 and Melan-A positivity, focal HMB-45 expression, and a low proliferative index, consistent with a cellular blue nevus.
Conclusion: Both cases emphasize the diagnostic dilemmas posed by rare benign melanocytic lesions, which can closely resemble melanoma. Careful correlation of histologic features with IHC markers is crucial to avoid overdiagnosis and unnecessary aggressive management. Awareness of these entities is essential for pathologists to ensure accurate classification and appropriate clinical decision-making.

Keywords: epithelioid melanocytoma, blue nevus, skin.

GIANT CELL TUMOR OF BONE: TWO DECADES OF SURGICAL MANAGEMENT AT A SINGLE REFERRAL CENTER

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Introduction: Giant cell tumor of bone (GCTB) is a common locally aggressive tumor with unpredictable behavior; thus, the selection of the most appropriate surgical procedure is challenging. Our aim was to review our 20-year experience in surgical management of GCTB and identify possible prognostic factors that might influence treatment decisions.
Material and methods: We analyzed 80 patients with histologically confirmed GCTB, treated at our institution between 2000 and 2020. Patients' demographics, tumor location, Campanacci staging, treatment and outcomes were reviewed, and multivariate predictors of recurrence-free survival were analyzed.
Results: Out of the 80 patients, 62.5% were female, with median age of 35 years. The most common tumor location was tibia (36.3%), followed by the femur (20.0%). At presentation, 50% were Campanacci stage 3. Primary treatment included curettage and adjuvant treatment in 57.5%, and resection with amputation in 42.5%. Chi-Square test showed that recurrence rates were significantly associated with Campanacci stage (χ^2 =7.48, df=2, p=0.024). A significant linear trend was confirmed (p=0.008). In multivariate logistic regression, location was the only independent predictor of recurrence. Patients with appendicular tumors had significantly lower odds of recurrence compared to axial tumors (OR =0.077, 95% CI, p=0.040). In Cox regression, axial location (HR 17.5, 95% CI 2.7–112.3, p=0.003) and non-definitive treatment (HR 4.8, 95% CI 1.1–20.8, p=0.037) were independent predictors of recurrence-free survival.
Conclusions: In our cohort, higher Campanacci stage correlated with recurrence, but axial location was the strongest predictor. Non-definitive treatment further reduced recurrence-free survival, emphasizing the impact of site and surgical approach on outcomes.

Keywords: giant cell tumor of bone, recurrence, curettage, bone resection, adjuvant therapy.
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SOFT TISSUE SARCOMAS IN NORTH MACEDONIA: A DECADE OF EPIDEMIOLOGICAL INSIGHTS

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Background: Soft tissue sarcomas (STS) are rare and heterogeneous malignancies that require a multidisciplinary approach to achieve optimal outcomes. This 10-year retrospective study aimed to evaluate the clinicopathologic features and prognostic factors in a single-center cohort.
Material and methods: We retrospectively searched our database for ICD-10 codes C47 and C49 between 2015 and 2024. Dermatofibrosarcoma protuberans (n=53), atypical lipomatous tumor/well-differentiated liposarcoma (n=78), and retroperitoneal, visceral, or peritoneal sarcomas (n=87) were excluded. A total of 190 patients met the criteria. Clinical and pathologic data were recorded, and survival outcomes were analyzed using Kaplan–Meier and Cox regression.
Results: The cohort consisted of 104 males and 86 females, with a median age of 60. The most common histologies were liposarcomas (26.3%), undifferentiated sarcomas (21.1%), and fibroblastic/myofibroblastic sarcomas (18.4%). Most tumors were grade 3 (62.1%) and stage III at diagnosis (58.0%). Median overall survival (OS) was 56 months (95% CI 40.5–71.5), with 82% 1-year, 64% 3-year, and 48% 5-year survival rates. Stage-stratified OS: not reached for stage I, 66 months for stage II, 47 months for stage III, and 31 months for stage IV. Significant difference in survival was found in females ($p = 0.033$) and low-grade sarcomas ($p = 0.042$). Median recurrence-free survival (RFS) was 43 months. Age was the only independent predictor of recurrence in Cox regression (HR 1.023/year, $p = 0.004$).
Conclusion: In our cohort, advanced stage, high grade, and male sex were associated with worse survival, while age independently predicted recurrence of soft tissue sarcomas.

Keywords: soft tissue sarcoma, epidemiology, survival analysis, recurrence-free survival, prognostic factors.

ENDOMYOCARDIAL BIOPSY IN THE REPUBLIC OF NORTH MACEDONIA

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Introduction: The heart transplant program in North Macedonia was successfully established amid the COVID-19 pandemic crisis.
Material and methods: We hereby present our center's initial experience during the period of May 2020 and May 2025. Eleven transplantations were performed, 3 patients succumbed to graft failure and severe infectious complications, and 8 patients have preserved graft function, undergoing regular follow-up. According to current guidelines and best practices, endomyocardial biopsy (EMB) remains gold standard to reliably diagnose rejection. At our institution, EMB was performed under fluoroscopy guidance in all patients using 7F pre-curved endomyocardial bioptome via right internal jugular vein cannulation under local anesthesia. There were no major periprocedural complications. Biopsy specimens were handled according to established laboratory protocols, stained with H&E, immunohistochemistry ordered for CD4, CD8, CD20, CD 68 and C4d to assess for antibody-mediated rejection. Histopathological analysis was performed at the Institute of Pathology, Faculty of Medicine in Skopje, and reported according to revised International Society for Heart and Lung Transplantation grading criteria.
Results: Mild acute cellular rejection (ACR 1R) was noted in 2 patients, asymptomatic ACR 2R in 3 patients - treated with increased immunosuppression. Mild antibody-mediated rejection (AMR 1R) was noted in 2 patients and 3 patients remained free of rejection. There were no hemodynamically significant allograft rejection episodes.
Conclusion: Despite low complication rates, current transplant protocols imply high frequency of EMBs. Additionally, there is suboptimal inter-observer agreement among pathologists regarding interpretation of findings. We speculate that emerging non-invasive methods of graft surveillance could serve as potential surrogates to EMBs, thereby minimizing patient discomfort without compromising graft function.

Keywords: heart transplantation, endomyocardial biopsy, allograft rejection.

EXTRAUTERINE LIPOLEIOMYOMA: REPORT OF TWO CASES AND LITERATURE REVIEW

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Introduction: Extrauterine lipoleiomyomas are extremely rare benign tumors composed of smooth muscle cells and mature adipose tissue. They may arise in retroperitoneal or intraperitoneal locations and can mimic malignant or fat-containing lesions, posing a diagnostic challenge.
Case Presentation and Methods: We report two cases in postmenopausal women. Case 1 involved a 50-year-old woman undergoing hysterectomy for symptomatic uterine leiomyomas, with a concomitant retroperitoneal mass. Case 2 involved a 70-year-old woman presenting with a large intraperitoneal abdominal mass. Both lesions were surgically excised. Gross examination, histopathology, and immunohistochemistry were performed, including SMA, S100, HMB-45, Melan-A, and Ki-67 staining.
Results: Both tumors displayed fascicles of bland smooth muscle cells interspersed with lobules of mature adipose tissue. S100 was positive in adipose tissue, SMA was positive in smooth muscle, and HMB-45 and Melan-A were negative. No atypia, mitoses, or necrosis were identified. Ki-67 proliferation index was low (~1%).
Conclusion: Extrauterine lipoleiomyomas are rare, benign lesions that should be considered in the differential diagnosis of fat-containing abdominal masses. Accurate diagnosis relies on histopathology and immunohistochemistry to distinguish them from malignant or melanocytic tumors. Complete surgical excision is curative, with excellent prognosis.

Keywords: lipoleiomyoma, extrauterine, retroperitoneal tumor, intraperitoneal tumor, case report.

CLINICOPATHOLOGICAL CONSIDERATIONS IN THE DIAGNOSIS OF SYMPTOMATIC AND INCIDENTAL PULMONARY HAMARTOMAS

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Introduction: Pulmonary hamartomas (PHs) are the most prevalent benign lung tumors. They are commonly asymptomatic and are incidentally discovered during evaluation for other diseases or during autopsy.
Materials and Methods: We conducted a retrospective study of surgical resections over a five-year period involving patients diagnosed with PHs at the Institute of Pathology in Skopje, with the aim to assess their clinicopathological characteristics. The review included 11 cases, from which clinical data such as age, sex, tumor size, laterality, and initial clinical diagnosis were collected. Histopathological assessment was performed using hematoxylin-eosin-stained slides. Furthermore, gross features and their correlation with imaging findings were documented.
Results: The group included 7 males and 4 females, aged between 40 and 67 years, with an average age of 57.3 years. Tumor sizes ranged from 1.2 to 6.0 cm, with a mean size of 2.64 cm. The tumors were located in the left lung in 4 cases and in the right lung 7 cases. Most lesions appeared as solitary, lobulated masses that were grey-white with translucent areas, and the imaging studies showed well-circumscribed nodules; some exhibited characteristic fat or calcifications. Clinically, 2 patients were suspected of malignancy, and the remaining were described as nonspecific tumor lesions. Histologically, all tumors showed cartilage, adipose tissue, fibrous stroma, and entrapped epithelium.
Conclusion: Pulmonary hamartomas typically affect middle-aged to older adults with a slight male predominance. Tumors are usually small and solitary, with gross and imaging features closely correlated. Prognosis is excellent, though rare associations such as neuroendocrine hyperplasia or bullous changes highlight diagnostic variability.

Keywords: pulmonary hamartoma, benign lung tumor, tumor size, clinicopathological study.

RARE HISTOLOGICAL VARIANTS OF PAPILLARY THYROID CARCINOMA: INSIGHTS FROM AN INSTITUTIONAL SERIES

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Background: Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy. While the classic type predominates, several rare histological variants occur and show distinct clinicopathological features. Their recognition is essential for accurate diagnosis and prognosis.
Aim: To evaluate the clinicopathological characteristics of rare PTC variants diagnosed in our institution between 2023 and 2025.
Materials and Methods: A retrospective analysis was performed on 11 rare PTC cases diagnosed during 2023–2025. All tumors were examined microscopically, and some were additionally confirmed by immunohistochemistry. Clinical and pathological data, including age, sex, histological subtype, and tumor stage, were classified according to the 4th edition of the WHO Classification of Endocrine Tumours and the UICC 8th edition of TNM system.
Results: The series included 6 tall-cell, 2 oncocytic, 2 Warthin-like, and 1 diffuse sclerosing variant. Patients were mainly female (n = 10), with a single male case of tall-cell variant. Age ranged from 41 to 71 years, except for the diffuse sclerosing variant, which occurred in a 24-year-old female. All tumors were stage I at presentation, with no lymph node metastases.
Conclusions: Rare PTC variants affect predominantly females and may occur across a wide age range. In this series, all cases were detected at an early stage without nodal involvement, suggesting a favorable prognosis. Microscopic examination continues to be the primary method of diagnosis, with immunohistochemistry providing supplementary confirmation.

Keywords: papillary thyroid carcinoma; tall-cell variant; oncocytic variant; Warthin-like variant; diffuse sclerosing variant

SQUAMOUS CELL CARCINOMA ARISING IN A KELOID SCAR: A CASE REPORT AND LITERATURE REVIEW

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Introduction: Keloids are characterized by abnormal fibroblast proliferation and excessive collagen deposition. While typically benign, they have been recognized as potential predisposing factors for cutaneous neoplasia.
Case Presentation: We present a rare case of squamous cell carcinoma (SCC) arising within a keloid scar in a 38-year-old female with a history of exuberant keloid formation on the feet. Histopathological examination of the excised lesion revealed moderately differentiated SCC developing within keloid tissue, marked by invasive nests of atypical squamous cells and keratin pearl formation embedded in dense keloidal stroma.
Conclusion: Although exceedingly rare, malignant transformation of keloid scars into SCC can occur, particularly in lesions exposed to chronic irritation, inflammation, ulceration, repeated trauma, or ultraviolet radiation. Clinicians should maintain a high index of suspicion when evaluating morphological changes in long-standing keloids. Early biopsy of suspicious lesions is crucial for timely diagnosis and appropriate management.

Keywords: squamous cell carcinoma, keloid scar, histopathology, chronic inflammation, skin lesion.

SCHWANNOMA OF THE BREAST: A CASE REPORT

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Background: Schwannomas are common benign nerve sheath tumours arising from the peripheral nerve sheath and commonly affect young adults. Typically solitary, they usually develop on the limbs, head and neck. Breast is a rare location of schwannoma.
Case presentation: We report a case of 55-year-old woman presented with one year history of palpable and painful lump in the right breast. An ultrasound revealed round 2 cm solid hypoechoic nodule with well-defined, regular margins. Fibroepithelial tumor was suspected and tumorectomy was performed without a preoperative needle biopsy.
Gross examination revealed an encapsulated, tan-white tumor. Histological examination showed a well-circumscribed benign proliferation consisting of two distinguished zones: hypercellular Antony A areas along with hypocellular Antony B areas. Immunohistochemically, tumor cells showed strong and diffuse positive staining for S-100 and Vimentin, favoring the diagnosis of schwannoma.
Conclusion: Considering the unusual location and rare occurrence of schwannomas, this case report serves as a reminder to include them in differential diagnoses of breast tumors. Breast schwannomas show no definite mammographic or ultrasonographic features, and an imaging diagnosis is impossible. They can be mistaken for a range of benign to malignant tumors such as fibroadenoma, phyllodes tumour or breast carcinoma.

Keywords: breast neoplasms, schwannoma, peripheral nerve sheath tumor, differential diagnosis.

EOSINOPHILIC ULCER – PRESENTATION OF TWO CASES

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Introduction: Eosinophilic ulcers are rare, benign, reactive, and often self-limiting lesions of the oral cavity, which clinically resemble carcinoma.
Case Reports:
Case 1: A 71-year-old woman presented with an unclear ulcerative lesion with a crater-like appearance on the right edge of the tongue that had persisted for one month. The surgical specimen was an incisional biopsy material that was consisted of an elliptical section of mucosa measuring 1.5 x 1.2 cm. An ulceration measuring 0.8 x 0.6 cm was present centrally on the surface, 0.1 cm distant from the peripheral resection margin.
Case 2: A 79-year-old man presented with an erosive-ulcerative persistent lesion on the right edge of the tongue, and clinical evidence of irritation from a denture. The surgical material was an elliptical piece of mucosa measuring 1.5 x 0.7 cm. An ulceration measuring 0.6 x 0.4 cm was seen centrally on the surface, 0.1 cm away from the peripheral resection margin.
Microscopic analysis in both cases showed ulcerated tongue mucosa, under which a rich mixed inflammatory infiltrate with a multitude of eosinophils was present, penetrating deeply and between the muscle bundles of the tongue present in the specimen.
Discussion: Eosinophilic ulcer of the oral mucosa is a benign, rare, self-limiting, and generally asymptomatic lesion that shows spontaneous regression. Its etiopathogenesis is still uncertain, but trauma seems to play a fundamental role in its occurrence.
Conclusion: Although the ulcer is benign in nature, a biopsy is necessary to rule out malignancy and to avoid overtreatment in patients.

Keywords: eosinophilic ulcer, oral cavity, self-limiting.

MORPHOLOGICAL AND DEMOGRAPHIC PROFILE OF HEAD AND NECK LESIONS IN NORTH MACEDONIA: A RETROSPECTIVE ANALYSIS

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Background: Regional epidemiological data on head and neck (H&N) lesions in the Republic of North Macedonia are limited.
Objective: To describe the morphological spectrum and demographic correlations of H&N lesions diagnosed at a single histopathology center (UKRO) between July 2024 and July 2025.
Methods: A retrospective analysis of 800 histological specimens was made. Lesions were classified according to the WHO criteria. Statistical analyses included χ^2 test, Student's t-test and Fisher's exact test with Bonferroni correction (SPSS v.29; α=0.05). Staging analysis was performed for confirmed malignancies.
Results: Malignant lesions accounted for 27.5% (n=220) of cases and were significantly more frequent in patients >60 years ($p<0.001$). The larynx was the predominant site of malignancy (53%; $p<0.001$). Squamous cell carcinoma (SCC) comprised 92.7% of malignant tumors (n=202). Of these, keratinizing SCC represented 79.2% (n=160; 95% CI: 73.1–84.6%), while non-keratinizing SCC accounted for 20.8% (n=42). Two-thirds of laryngeal SCCs presented at stage II–III (66.8%; n=135/202). Benign lesions comprised 55.3% (n=442) and included vocal cord polyps (n=131), keratotic papillomas (n=95), nasal polyps (n=33), granulation tissue (n=33), cholesteatomas (n=22), follicular adenomas (n=11) and 97 other rare entities. Premalignant/dysplastic changes were identified in 4% of cases (n=32).
Conclusion: This single-center series demonstrates a high prevalence of keratinizing laryngeal SCC and a substantial proportion of cases diagnosed at an advanced stage (II–III). Limitations include the retrospective design, incomplete clinical risk-factor data and single-center scope. Prospective, multicenter studies with molecular analyses are warranted.

Keywords: head and neck lesions; squamous cell carcinoma; larynx; epidemiology; North Macedonia.

POTENTIAL PATHOGENIC VARIANTS IN *FANCM* AND *MUTYH* GENES AND INTERGENIC REGIONS TO BREAST CANCER RISK

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Introduction: Breast cancer (BC) is the most common cancer in women, with more than 2 million new cases diagnosed yearly. The already known likely pathogenic or pathogenic germline mutations for breast cancer and/or ovarian cancer (OC) can explain fewer than half of all familial BC and/or OC.
Aim of the study: Increasing diagnostic yield by accumulating important data on potential breast cancer susceptibility gene candidates (FANCM and MUTYH), and providing a better understanding of BC. Recently, it became clear that only a 7% of disease-associated SNPs are located in protein-coding regions, while 93% are located in gene regulatory regions or in intergenic regions.
Materials and Methods: We conducted a retrospective study analyzing clinical and molecular characteristics of 142 breast cancer patients from January 2022 to December 2024, which were examined at the Institute of Pathology in Skopje. Genomic DNA was isolated using the innuPREP Blood-DNA-Kit (Analytik Jena). Next-Generation Sequencing was performed using the TruSight Cancer Panel (Illumina Inc.) on MiSeq.
Results: We found 29 carriers (20.4%) with the intergenic T>C variant (g.51549496), which is classified as highly pathogenic for an increased risk of developing prostate cancer. Nine variants of unknown significance (VUS) (6.3%) were found in the MUTYH gene. In FANCM gene, we found 9 different VUS, including previously unreported variant in the FANCM gene c.4264A>C, p. (Ile1422Leu), which was only later published by Ambry Genetics.
Conclusion: Interpretation of this data support and contribute to work assessing the possible association between breast cancer risk and FANCM and MUTYH genes, as well as intergenic regions.

Keywords: breast cancer, next-generation sequencing, variants of unknown significance, intergenic regions.

ARTIFICIAL INTELLIGENCE IN HAEMATOPATHOLOGICAL DIAGNOSTICS

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The digitization of histological slides, together with the parallel advances in machine learning, has opened the door to the application of various artificial intelligence (AI) models in everyday diagnostics. This report reviews routine tasks in haematopathological practice that could potentially be supported by supervised, assistive neural networks. Of particular interest is the discovered ability of AI to "see" and predict, with relatively high accuracy, correlations between major mutations and the phenotype of H&E-stained slides. The first steps of the Department of General and Clinical Pathology at the Medical University – Sofia towards the introduction of AI-assisted haematopathological diagnostics on trephine biopsy materials are presented. Current challenges that hinder the widespread implementation of AI in histological practice are also discussed.

Keywords: AI, haematopathology, neural networks

NEUROENDOCRINE NEOPLASMS IN RARE ANATOMICAL SITES: A FIVE-YEAR RETROSPECTIVE CASE SERIES

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Background: Neuroendocrine neoplasms (NENs) most frequently arise in the gastrointestinal and pulmonary systems. NENs in rare anatomical sites pose diagnostic challenges due to overlapping morphology and low clinical suspicion. This study describes the clinicopathological features of NENs in uncommon sites discovered in a five-year period.
Methods: We retrospectively analyzed NENs diagnosed at the Institute of Pathology in a 5-year period (2019-2024). Data included demographics, tumor histology, immunohistochemical characteristics, Ki-67 index, and clinical details.
Results: Among 215 diagnosed cases of NENs, 11 were identified in uncommon anatomical sites: urinary bladder (n=4), uterine cervix (n=2), uterine corpus (n=2), breast (n=2), and ovary (n=1). There were 8 females and 3 males, aged 32 to 74 years. All tumors exhibited neuroendocrine morphology with 100% synaptophysin and chromogranin A expression in 81.8%. Except for two breast tumors (graded G1 and G2), all were high-grade NECs, with Ki-67 indices ranging from 50% - 90%. One case was initially misclassified as a poorly differentiated non-neuroendocrine carcinoma, underscoring the diagnostic pitfalls due to morphologic overlap. The ovarian and uterine corpus cases represent the rarest sites in this series, with high-grade NECs in these locations being exceptionally uncommon in the literature. Diagnosis in all cases relied on broad IHC panels. Treatment varied by site and tumor grade.
Conclusion: NENs in uncommon anatomical sites remain diagnostically challenging due to rarity and nonspecific morphology. This case series contributes to the limited literature and reinforces the importance of including NENs in the differential diagnosis of poorly differentiated tumors. Comprehensive immunohistochemical workup is crucial for accurate classification and clinical management.

Keywords: neuroendocrine neoplasms (NENs); rare anatomical sites; high-grade neuroendocrine carcinoma; immunohistochemistry; diagnostic challenges; Ki-67 index; case series; urinary bladder; uterine cervix; uterine corpus; breast; ovary

MISMATCH REPAIR STATUS IN COLON CANCER: A SINGLE-CENTRE EXPERIENCE FROM NORTH MACEDONIA

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Introduction: Mismatch repair (MMR) status in colon cancer (CC) patients has important value in prognostic stratification, predicts response to adjuvant chemotherapy, identifies patients who can benefit from immunotherapy and screening for Lynch syndrome. In this study, we aimed to assess MMR status in stage II and III CC patients and to evaluate its relationship to clinicopathological characteristics as a single center experience.
Materials and methods: This retrospective study included 91 CC patients whose specimens were obtained from surgical colectomy material between 2018-2021 at the University Clinic for Digestive Surgery in Skopje, the Republic of North Macedonia. MMR status was assessed by immunohistochemistry for MLH1, MSH2, MSH6 and PMS2 performed on Roche Ventana Benchmark XT autostainer.
Results: Deficient MMR (dMMR) was observed in 16 cases (17.6%) most frequently with MLH1/PMS2 loss (7), followed by isolated loss of MLH1 (3), MSH2 (2), and PMS2 (2), as well as MSH2/MSH6 loss (1) and MLH1/MSH6/PMS2 loss (1). Proficient MMR (pMMR) was observed in 75 cases (82.4%). dMMR was significantly associated with right-sided tumors ($p<0.0001$), stage II disease ($p=0.002$), absence of lymph node involvement (pN0, $p=0.008$), absence of lymphatic invasion (pL0, $p=0.016$), and mucinous histology ($p<0.0001$). No significant associations were found between MMR status and age, sex, tumor grade, vascular invasion, relapse, or mortality.
Conclusion: dMMR status was strongly associated with right-sided tumors, stage II disease, and mucinous histology, with MLH1/PMS2 loss being the most frequent pattern. MMR testing should be routinely included in pathology reports.

Keywords: colon cancer, mismatch repair, immunohistochemistry, deficient, proficient

SIGNIFICANCE OF PCR DIAGNOSTICS FOR THE DETECTION OF KRAS/NRAS ANALYSIS

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Background: The most common oncogene in human cancer is the RAS oncogene, which occurs in 20-25% of all human tumors. Chromosome 12 carries the RAS gene, which encodes a protein involved in the transmission of signals that determine cell proliferation and differentiation. If a mutation occurs in the KRAS and NRAS genes, disrupted and uncontrolled activation happens, resulting in continuous cell proliferation in the tissue, and the development of colon tumors. Colorectal cancer has been shown to be a leading malignant tumor of the digestive tract that can occur equally in both men and women. In the course of testing, mutations in codons 12 and 13 of the RAS gene are most often activated. Somatic mutations of the KRAS gene are activated in 40% of colorectal cancer cases while NRAS is activated in only 7%.
Material and methods: To demonstrate the presence of KRAS and NRAS mutations, it is necessary to perform diagnostic testing to determine which patients are candidates for targeted therapy of metastatic cancer. Testing is done on FFPE tumor tissue samples. PCR testing represents one of the most advanced methods for detecting the presence of mutations of a particular gene.
Conclusion: By comparison of the results obtained using AmoyDx and Diatech Pharmacogenetis detection tests, it is concluded that detection tests with a greater range of gene loci have a higher rate of mutation positivity in the RAS gene.

Keywords: KRAS, NRAS, FFPE tissue, PCR diagnostic, frequency of mutations examined.

RARE OCCURRENCE OF CILIATED METAPLASIA IN THE URETER: A CASE REPORT AND LITERATURE REVIEW

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Background: Ciliated epithelial cells are exceedingly rare in the urinary tract, which is predominantly lined by urothelium. These cells have been documented almost exclusively in the male urethra. We report an unusual case of ciliated pseudostratified columnar epithelium in the ureter of a 58-year-old woman with a history of nephrolithiasis.
Case presentation and methods: Two ureteral biopsy fragments were examined with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS) and Alcian blue stains. An immunohistochemical panel including GATA3, MCA, and AMACR was used to characterize the ciliated epithelium.
Results: Microscopic examination revealed urothelium with ciliated pseudostratified columnar metaplasia. The lamina propria exhibited a prominent mixed inflammatory infiltrate. Alcian blue highlighted apical vacuoles in some cells, consistent with mucin production. Immunohistochemistry demonstrated GATA3 and MCA negativity and AMACR positivity in rare, scattered cells of the metaplastic epithelium.
Conclusion: Ciliated pseudostratified columnar metaplasia of the ureter is exceptionally rare. The observed immunoprofile, along with the association with nephrolithiasis, supports a metaplastic response potentially related to chronic irritation and altered mucociliary clearance. Further studies are warranted to elucidate its incidence, pathogenesis, and clinical significance.

Keywords: urothelium, ciliated cells, metaplasia, ureter, nephrolithiasis.

CLEAR CELL ADENOCARCINOMA OF THE BLADDER: A RARE DIAGNOSTIC CHALLENGE

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Introduction: Clear cell adenocarcinoma of the bladder is an uncommon type of bladder cancer, accounting for less than 1% of all bladder neoplasms. It is thought to originate from nephrogenic, Müllerian, or urachal remnants, although its definitive embryogenesis remains widely debated.

Case presentation: We present the case of a 77-year-old female with complaints of intermittent gross hematuria. Cystoscopy revealed a 2 cm lesion encroaching upon the right ureteral orifice. A transurethral resection was performed. Histologically, the tumor mass was composed of monotonous cells with clear cytoplasm, arranged in papillary and tubular structures. The lesion exhibited an infiltrative growth pattern into the smooth muscle layer of the bladder.

Immunohistochemistry showed positivity for CK7, CK20, and CDX2. The tumor was negative for GATA3, p63, PAX8, TTF-1, and Napsin A; PAX2 and PTEN expression were retained. No components of classical urothelial neoplasia were identified, and there was no history or clinical evidence of renal or gynecological disease. Based on these findings, the case was diagnosed as clear cell adenocarcinoma of the bladder.

Discussion: Clear cell adenocarcinoma of the bladder is an extremely rare entity. This case highlights the diagnostic complexity of the disease, as it can exhibit significant morphological and immunohistochemical overlap with neoplasms of Müllerian and mesonephric origin. It is important to raise clinical awareness of rare cancer subtypes with prognostic significance, which may present a diagnostic challenge.

Keywords: clear cell adenocarcinoma, immunohistochemistry, bladder cancer.

A DECADE OF TESTICULAR TUMORS IN NORTH MACEDONIA: EXPERIENCE FROM THE LARGEST NATIONAL PATHOLOGY CENTER

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Background: Testicular cancer is a rare malignancy, accounting for approximately 1% of adult neoplasms, yet it remains the most common cancer in young men. Despite its clinical significance, national epidemiological data have not been systematically reported.
Aim: This study aimed to evaluate the spectrum of testicular tumors diagnosed over the past decade at the largest national pathology center.
Materials and Methods: We retrospectively analyzed 274 testicular specimens diagnosed at the Institute of Pathology, Skopje, between 2014 and 2025. After excluding consultation cases and intraoperative biopsies, 242 orchiectomy specimens were included in the final analysis.
Results: Among 242 operated patients, tumors were confirmed in 201 cases. The median age was 35 years (range: 1–84). Germ cell and sex cord–stromal tumors accounted for 186 cases, with seminoma being the most frequent subtype (88 cases, 36.4%), followed by mixed germ cell tumor (74 cases, 30.6%). Less common subtypes included embryonal carcinoma (n=10, 4.1%), teratomas (n=4, 0.8%), yolk sac tumors (n=2, 0.8%) and sex cord tumors (n=8, 3.3%). Fifteen cases were classified as other malignancies or rare lesions. Of 177 staged tumors, stage IB predominated (59.3%), followed by stage IA (38.4%), with higher stages being rare.
Conclusion: To our knowledge, this is the first national overview of testicular tumor distribution in North Macedonia. The predominance of early-stage tumors aligns with international data and underscores the importance of early detection, particularly in younger male patients. This study provides a foundation for future national registries and collaborative research. Further investigation into molecular markers and long-term outcomes is recommended.

Keywords: testicular tumors; germ cell tumors; orchiectomy; epidemiology; North Macedonia.

MELANOMA WITH CARTILAGINOUS TRANSDIFFERENTIATION MIMICKING DIABETIC ULCER: A CASE REPORT AND LITERATURE REVIEW

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Introduction: Malignant melanoma is known for its morphological heterogeneity and diverse histopathological presentations. Among its rare subtypes, melanoma exhibiting cartilaginous transdifferentiation is exceptionally uncommon.
Case Presentation: We present the case of a 73-year-old male with a history of diabetes who underwent amputation of the fifth pedal digit. The lesion had been misdiagnosed and managed as a diabetic foot ulcer for one year. Histopathological analysis revealed an ulcerated epidermis with underlying dermal nests of epithelioid to rounded atypical chondrocyte-like cells embedded in chondroid matrix. A small deep focus of conventional melanoma with scattered atypical melanocytes containing melanin pigment was present. Immunohistochemical staining showed strong positivity for S-100 and SOX-10. HMB-45 was positive in tumor cells located in the upper dermis, while Melan-A highlighted only a few scattered cells. BRAF mutation analysis revealed no pathogenic mutations. Based on these findings, a diagnosis of malignant melanoma with cartilaginous transdifferentiation was established.
Discussion: Melanoma with cartilaginous differentiation tends to occur in acral locations, particularly subungual regions. The primary differential diagnosis is chondrosarcoma. Although S-100 is expressed in both melanocytic and cartilaginous tissues, the use of additional melanocytic markers and BRAF mutation analysis can aid in confirming melanocytic origin and supporting the diagnosis of melanoma.
Conclusion: Clinicians should consider this rare melanoma type in cases of non-healing acral lesions. Accurate diagnosis relies on a combination of histopathological evaluation and immunohistochemical profiling, which remains the gold standard.

Keywords: malignant melanoma, cartilaginous transdifferentiation, histopathological evaluation.

PRIMARY SINONASAL MENINGIOMA MIMICKING BENIGN NASAL LESIONS - A CASE REPORT AND LITERATURE REVIEW

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Introduction: Primary extracranial meningiomas are rare neoplasms, accounting for less than 2% of all meningiomas. The sinonasal tract represents an uncommon site of origin and frequently presents diagnostic challenges due to nonspecific clinical and radiological features.
Case Presentation: A 79-year-old male presented with a unilateral nasal cavity mass. Computed tomography revealed diffuse polypoid mucosal thickening with near-complete opacification of paranasal sinuses and obliteration of aeration. Histopathology showed a circumscribed neoplastic proliferation arranged in lobular and whorled patterns beneath intact respiratory epithelium. Tumor cells displayed uniform morphology with oval nuclei, eosinophilic cytoplasm, and inconspicuous nucleoli. Psammoma bodies and delicate vascular channels were present. Necrosis, nuclear atypia, and mitotic activity were absent. Immunohistochemistry showed strong positivity for epithelial membrane antigen (EMA), vimentin, p63, and progesterone receptor, while cytokeratin AE1/AE3, CD34, smooth muscle actin (SMA), S100, SOX10, desmin, and synaptophysin were negative. The proliferative index (Ki-67) was <5%.
Discussion: Extracranial meningiomas are rare neoplasms with poorly understood histogenesis, presumably arising from displaced meningothelial cells during embryonic development. Sinonasal meningiomas may mimic other nasal masses including nasal polyps, inverted papilloma, olfactory neuroblastoma, or carcinoma. In this case, the morphological features combined with the supportive immunohistochemical profile confirmed the diagnosis of WHO Grade I meningothelial meningioma with angiomatous features.
Conclusion: Primary sinonasal meningioma should be included in the differential diagnosis of sinonasal masses. Accurate recognition through comprehensive histopathological and immunohistochemical analysis is essential for proper diagnosis and management.

Keywords: sinonasal meningioma, nasal cavity, histopathology analysis, immunohistochemistry .

IMMUNE LANDSCAPE OF FULLY REGRESSED PRIMARY CUTANEOUS MELANOMA: A CASE SERIES ANALYSIS

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Background: Tumor regression is an immune-mediated process that results in the partial or complete disappearance of malignant cells. Complete regression of primary cutaneous melanoma is rare and poorly understood. This study aimed to explore the immunohistochemical profile of tumor-infiltrating immune cells in fully regressed melanoma.
Methods: We analyzed five cases of completely regressed primary cutaneous malignant melanoma. Tissue sections were stained with H&E and subjected to immunohistochemical analysis using the EnVision FLEX technique. The antibodies used included CD4, CD8, CD20, CD23, CD25, CD31, CD34, CD68, S100A4, Podoplanin, HMB-45, Melan-A, S100 and SOX10.
Results: T cells were the predominant immune cells: CD8+ cells were concentrated in the regression and perivascular zones, while CD4+ cells were mainly intraepidermal. Histiocytes, including dendritic cells (CD68+, S100A4+, CD23+), were present in all cases. CD20+ B cells were scarce or absent. CD31 and CD34 showed increased vascular density in the regression zone. Podoplanin highlighted lymphatic vessels, with a capillary-to-lymphatic ratio of approximately 2:1. CD25 expression, indicating IL-2 receptor presence, was noted in dermal T cells and occasional residual tumor cells. Conventional melanocytic markers (HMB-45, Melan-A, S100) were negative, while SOX10 showed focal positivity.
Conclusions: Our findings suggest a significant role of immune–tumor cell interactions, potentially mediated by cytokines such as IL-2, in the process of melanoma regression. Further studies are warranted to understand these mechanisms and their clinical implications.

Keywords: tumor regression, cutaneous melanoma, immunohistochemistry.

UNMASKING INVISIBLE MELANOMA: HISTOLOGICAL AND IMMUNOHISTOCHEMICAL DIAGNOSIS OF COMPLETE PRIMARY REGRESSION

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Background: Complete regression of primary cutaneous malignant melanoma is an extremely rare phenomenon, believed to occur due to the host immune response. Diagnosing fully regressed melanoma is challenging, especially in the absence of a visible primary lesion.

Methods: We report three cases of completely regressed primary cutaneous malignant melanoma. Tissue sections were stained with hematoxylin and eosin (H&E) and analyzed immunohistochemically using melanocytic markers (Melan-A, HMB-45, S100) and immune cell markers (CD4, CD8, CD68).

Results: The first patient presented with regional lymph node metastasis and a regressed primary skin lesion identified concurrently. The second case involved a patient with a breast metastasis from melanoma, initially without an identifiable primary tumor; a regressed primary lesion was found one month later upon skin excision. The third patient was diagnosed with a fully regressed primary melanoma without evidence of metastasis to date.

Histological features across all cases included dermal fibrosis, lymphocytic infiltrates (CD8 +++, CD4 ++), pigment-laden macrophages (CD68 ++), ectatic blood vessels, and epidermal atrophy with flattened rete ridges. No atypical melanocytic cells were observed in the skin (Melan-A –, HMB-45 –, S100 –), while metastatic tissues were positive for these markers.

Conclusions: Fully regressed primary melanoma is rare and often only diagnosed after metastasis. Our cases, particularly the one without metastasis, highlight the importance of recognizing regressive features histologically and the crucial role of immunohistochemistry in confirming the diagnosis.

Keywords: tumor regression, cutaneous melanoma, immunohistochemistry.

THERAPEUTIC RESISTANCE IN SYNCHRONOUS ENDOMETRIOID CARCINOMAS: A CASE REPORT WITH A PATHOGENIC GERMLINE MUTATION IN PMS2

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Introduction: Synchronous gynecological malignancies, particularly endometrial and ovarian carcinomas, remain a diagnostic and therapeutic challenge, affecting approximately 2–10% of women with ovarian cancer. The role of mismatch repair (MMR) gene mutations, including PMS2, is increasingly recognized in the development and clinical course of such tumors.
Case report: We report the case of a 52-year-old woman diagnosed with synchronous endometrioid endometrial carcinoma (stage IA) and advanced endometrioid ovarian carcinoma (stage IIIC), both associated with a pathogenic PMS2 germline mutation (c.2007-2A>G). Following initial cytoreductive surgery, the patient received adjuvant carboplatin–paclitaxel chemotherapy. Despite treatment, early metastatic progression was detected in inguinal and hepatic regions, suggesting marked chemoresistance. Palliative inguinal resection and radiotherapy were undertaken for symptom control, but clinical benefit was limited.
Subsequent systemic therapy with cyclophosphamide and bevacizumab, delivered over eight and nine cycles respectively, failed to halt disease progression. The patient's condition steadily declined, culminating in death 18 months after diagnosis.
Conclusion: This case underscores the aggressive clinical trajectory and therapeutic resistance often seen in synchronous endometrial and ovarian carcinomas when linked to hereditary MMR mutations. It emphasizes the importance of genetic profiling, which can guide risk stratification, counseling, and the exploration of alternative therapeutic strategies, including immune checkpoint inhibitors or targeted approaches. Broader awareness and research into personalized management are crucial to improve outcomes in patients harboring MMR defects.

Keywords: endometrial carcinoma, ovarian carcinoma, PMS2 mutation, therapeutic resistance.

ULTRASTRUCTURAL ANALYSIS OF PLACENTAS FROM COVID-19 POSITIVE PREGNANT WOMAN: AN ELECTRON MICROSCOPY STUDY OF 15 CASES

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Introduction: Maternal SARS-CoV-2 infection has been associated with placental abnormalities, yet detailed ultrastructural changes remain underexplored.
Material and Methodes: To analyze the ultrastructural features of placental tissues from pregnant women diagnosed with COVID-19, with emphasis on trophoblastic integrity, vascular changes, and potential evidence of viral presence.
Fifteen placentas were collected from COVID-19 positive pregnant women at delivery. All patients were confirmed SARS-CoV-2 positive via RT-PCR. Ultrastructural findings were systematically evaluated and documented.
Results: Common findings included syncytiotrophoblast degeneration, thickening of the basal membrane, increased perivillous fibrin deposition, and stromal fibrosis. Endothelial damage and focal microthrombi were identified in fetal capillaries in several specimens. In 3 of 15 cases, virus-like particles resembling coronavirus morphology were observed within trophoblastic cytoplasm, although confirmatory immunolabeling was not performed. No specific organelles were targeted consistently across cases, and viral structures were not observed in fetal endothelial cells.
Conclusion: Placentas from SARS-CoV-2 positive pregnancies exhibit consistent ultrastructural changes suggestive of maternal and fetal vascular malperfusion, as well as trophoblastic stress. These findings may contribute to understanding the potential mechanisms of adverse pregnancy outcomes in COVID-19.

Keywords: COVID-19, pregnancy, placenta, electron microscopy, SARS-CoV-2.